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PART 1. S,S'-DIETHYL DITHIOMALONATE AS AN ETHANOL CARBANION EQUIVALENT IN MICHAEL REACTIONS

PART 2. CAMPHOR TO CEDROL - A CHEMICAL INVESTIGATION

by

© ISAAC VICTOR OPPONG

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
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OF DOCTOR OF PHILOSOPHY

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PART 2. CAMPHOR TO CEDROL - A CHEMICAL INVESTIGATION

submitted by ISAAC VICTOR OPPONG

in partial fulfilment of the requirements for the degree of DOCTOR OF PHILOSOPHY

Supervisor

E.V. Blackburn

George Kotovych

DATE: Jan. 26, 1974

TO MY WIFE AGNES, AND CHILDREN

ABSTRACT

The first part of this thesis describes the reaction of S,S'-diethyl dithiomalonate(I) with a number of α,β-unsaturated carbonyl compounds and the reduction of the adducts formed with a modified Raney nickel catalyst.

S,S'-Diethyl dithiomalonate(I) was found to react efficiently and under relatively mild conditions with 2-cyclohexen-1-one, ethyl acrylate, 2-cyclopenten-1-one, 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene(II), ethyl 2-carboethoxy-4-methyl-2-pentenoate(III), 3-penten-2-one, 3-carboethoxy-5,5-dimethyl-2(5H)-furanone(IV), methyl vinyl ketone, cis-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one(V) and 6-acetoxy-cis-bicyclo[3.2.0]hept-3-en-2-one(VI). The tertiary amine, 1,4-diazabicyclo[2.2.2]octane was found to be the most efficient base for the Michael reactions. In all the cases studied, except for methyl vinyl ketone only the mono-adduct of the general formula VII was formed. In the case of methyl vinyl ketone, the mono-adduct was obtained as the major product along with a small amount (10%) of the bis adduct VIII. S,S'-Diethyl dithiomalonate(I) did not react with α,β-unsaturated carbonyl compounds in which the β-carbon was fully substituted.

The adducts VII obtained were successfully reduced to the alcohol level (IX) using a modified Raney nickel catalyst. The use of S,S'-diethyl dithiomalonate(I) as a convenient source of an ethanol carbanion equivalent in Michael reactions has therefore been established in this work.

In the second part of this thesis the preparation of the bicyclic keto diester X, a potential synthetic precursor to cedrenoid sesquiterpenes, e.g. cedrol (XI), is described. The keto diester X was prepared in two forms, XII and XIII, by two different routes.

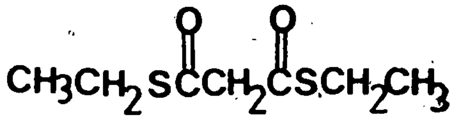
In the route to XII (+)-campholenic acid (XIV), obtained from d-10-camphorsulfonic acid was converted to the campholenic ester (XV). Photooxygenation of XV followed by reductive work up with sodium borohydride gave the allylic alcohol XVI. The allylic alcohol was also obtained from XV by epoxidation of the olefinic double bond followed by ring opening of the resulting epoxide XVII with lithium diisopropylamide. The epimeric alcohols XVI were subsequently oxidized with oxalyl chloride, dimethyl sulfoxide, and triethylamine to afford the enone XVIII. Addition of 1-nitropropane using potassium carbonate as base afforded the nitro ketone XIX, which was efficiently converted to the diketo ester XX by treatment with methanolic sodium methoxide and ozone followed by reductive work up with dimethyl sulfide.

Aldol condensation of XX using methanolic sodium methoxide in refluxing methanol afforded the bicyclic enone XXI as a single stereoisomer. 1,4-Addition of 3-butenylmagnesium bromide, in the presence of cuprous iodide gave the adduct XXII as an epimeric mixture. The ester side chain of XXII was converted to the olefin by reduction of XXII with sodium borohydride followed by addition of phenyl magnesium bromide to the resulting alcohols XXIII to afford the diols XXIV. Dehydration of the tertiary hydroxyl group, followed by oxidation of the secondary hydroxyl group afforded the keto diene XXV. Degradation of the two olefinic side chains was effected with ruthenium tetroxide. The resulting diacid was esterified with potassium carbonate and methyl iodide to afford the bicyclic keto diester XII as an epimeric mixture.

In the route to the bicyclic keto diester XIII compound XVI was treated with phenylmagnesium bromide to afford the diol XXVI. Treatment of the diol with oxalyl chloride, dimethylsulfoxide, and triethylamine resulted in the oxidation and dehydration of the secondary and tertiary alcohols, respectively, to give the dienone XXVII. Addition of 1-nitropropane to the dienone using potassium carbonate as base afforded the nitro olefin XXVIII which was efficiently converted to the diketo ester

XXIX in two steps by treatment with ruthenium tetroxide followed by esterification with potassium carbonate and methyl iodide.

Aldo[illegible]densation of XXIX was carried out with methanol[illegible]dium methoxide in refluxing methanol to give the bicyclic enone XXX, which was subjected to the treatment with 3-butenylmagnesium bromide and cuprous iodide to give a diastereomeric mixture of the 1,4-adducts XXXI. Degradation of the olefin was efficiently accomplished with ruthenium tetroxide. Esterification of the resulting acid then gave the bicyclic keto diester XIII as a diasteromeric mixture. Methods are under study for the conversion of XII and XIII to (+)-cedrol XI.



$CH_3CH_2S\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}SCH_2CH_3$

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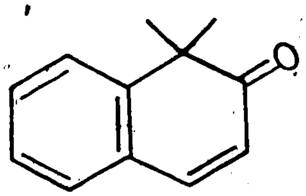

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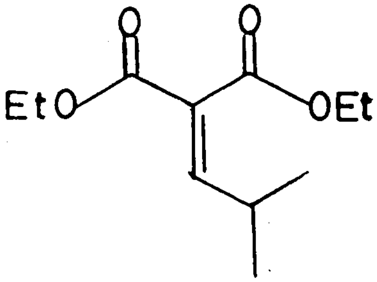

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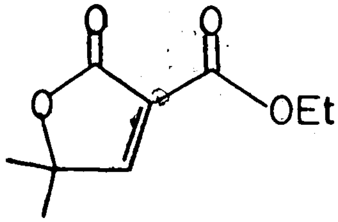

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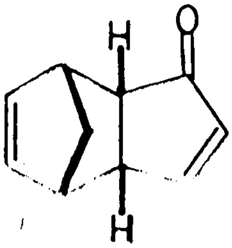

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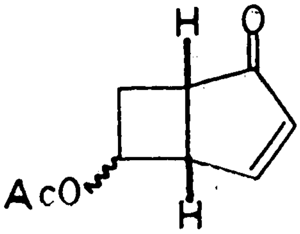

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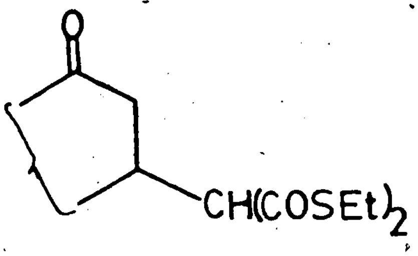

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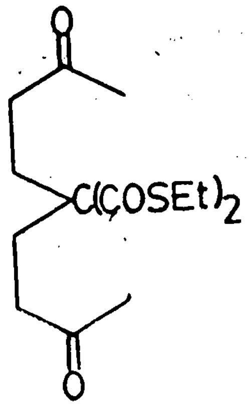

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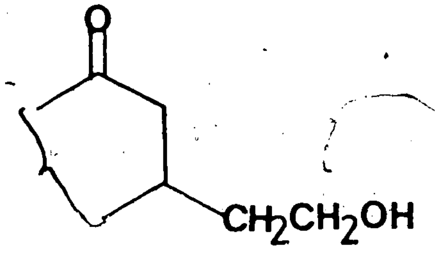

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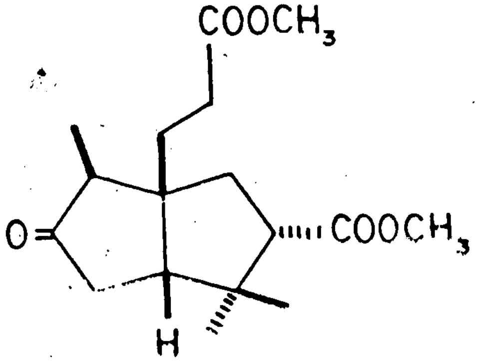

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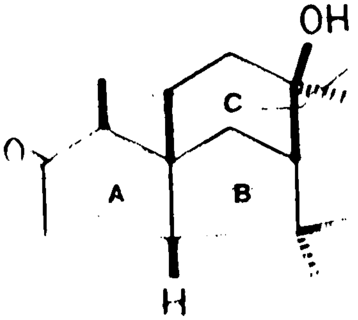

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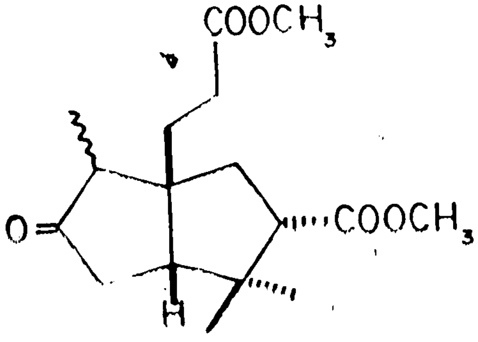

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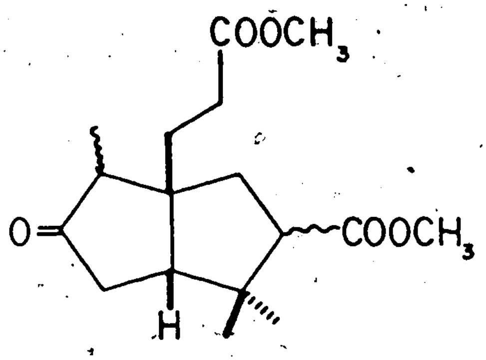

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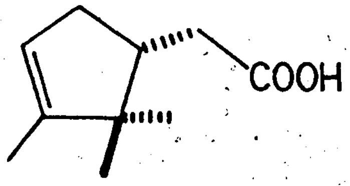

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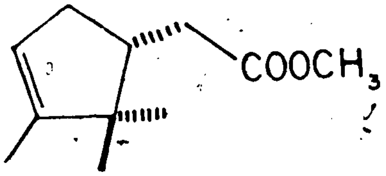

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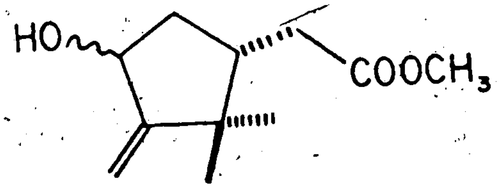

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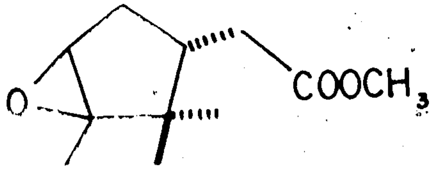

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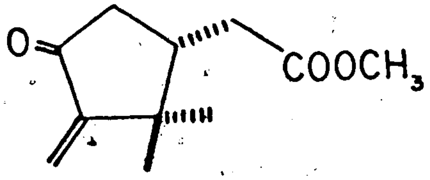

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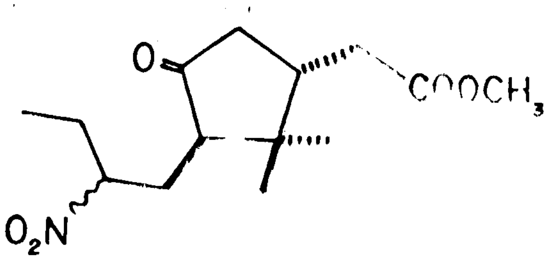

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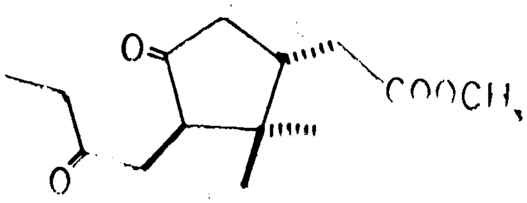

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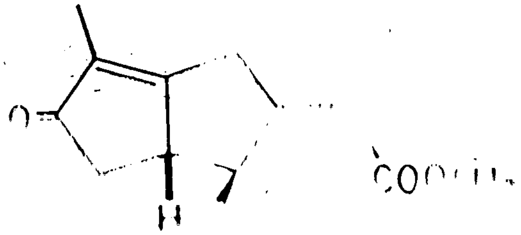

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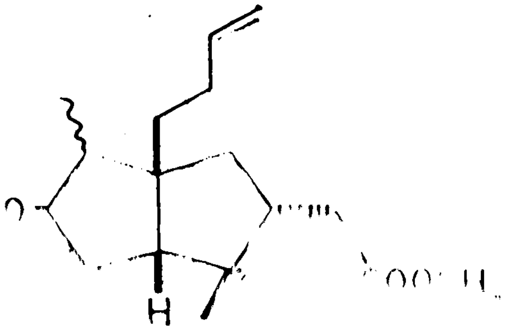

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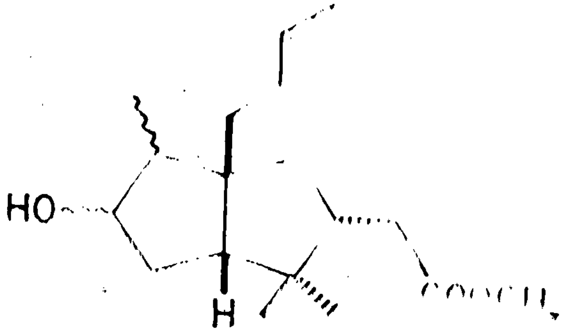

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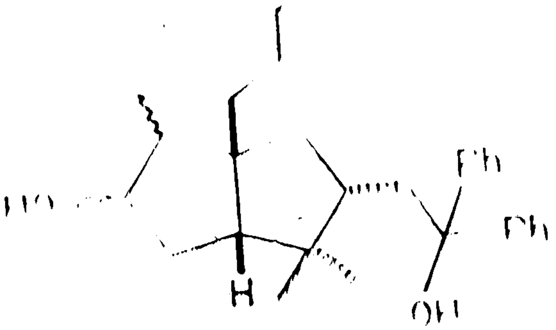

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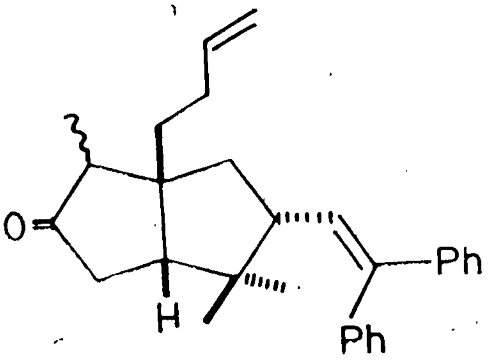

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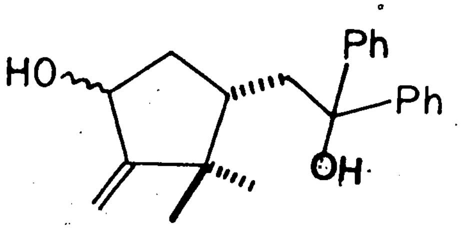

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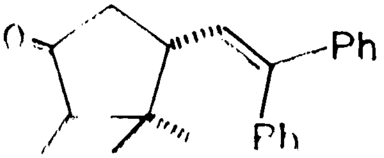

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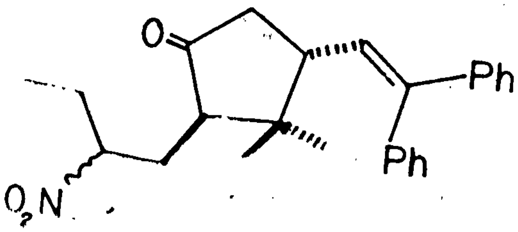

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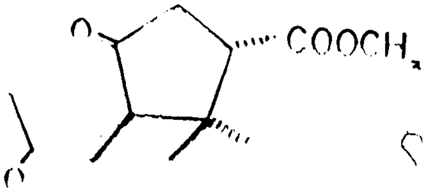

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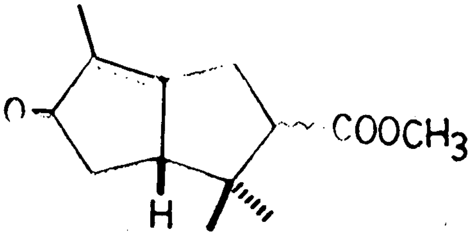

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PART 1. S,S'-DIETHYL DITHIOMALONATE AS AN ETHANOL CARBANION EQUIVALENT IN MICHAEL REACTIONS

INTRODUCTION

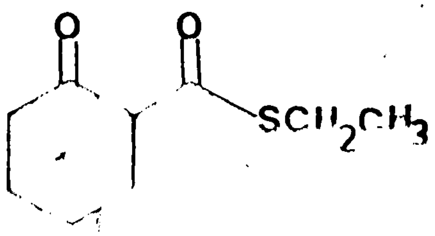
Since the remarkable discovery of the simultaneous desulfurizing and reducing action of Raney nickel (1) by Bougault and coworkers (2) and its subsequent extension by Mozingo's group (3), the reductive desulfurization by this reagent has found extensive use in organic syntheses. In an attempt to extend the desulfurizing reaction to the synthesis of aldehydes, Wolfrom and Karabinos (4) studied the Raney nickel reduction of thiolesters. They succeeded in the preparation of benzaldehyde, propionaldehyde, and aldehydo-D-ribose tetraacetate from their corresponding thiolesters. Concurrently, Prelog and coworkers (5,6) reported that the treatment of thiolesters with Raney nickel led exclusively to the formation of the corresponding alcohols. In 1948, Levin and his group (7,8) confirmed both findings and showed that the apparent discrepancy in the previous findings was due to the degree of reactivity of the Raney nickel used. They showed that with a standard Raney nickel catalyst under normal conditions the corresponding alcohols are formed from the thiolesters whereas, with partially deactivated Raney nickel (e.g. by boiling in acetone), the aldehydes are produced in satisfactory yields.

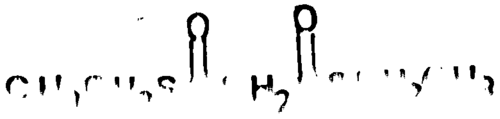
In their recent work on the dithiol diester version of the Dieckmann condensation (9), Liu and Lai (10) observed that β-keto thiolesters undergo facile dealkylthiocarbonylation reactions when treated with Raney nickel under virtually neutral conditions. For example, when the β-keto thiolester 1 was treated with excess W-2 Raney nickel (11) in ethanol at room temperature, it underwent clean removal of the thiolester moiety, resulting in the exclusive formation of cyclohexanone.

Two conclusions readily emerge from the experimental results on the Raney nickel reduction of thiolesters:

1. Raney nickel reduces thiolesters to either alcohols or aldehydes depending upon the degree of its reactivity.
2. The thiolester group is completely cleaved by Raney nickel when it is attached to the alpha-carbon of a ketone carbonyl.

Based on these experimental results, it was suggested (12) that the treatment of a 1,3-dithiol diester with Raney nickel should in principle result in the removal of one thiolester group with concomitant reduction of the other to the aldehyde or alcohol level. This hypothesis was substantiated experimentally using a variety of S,S'-diethyl dithiomalonate (2) derivatives, which were readily prepared by alkylation of the parent molecule.





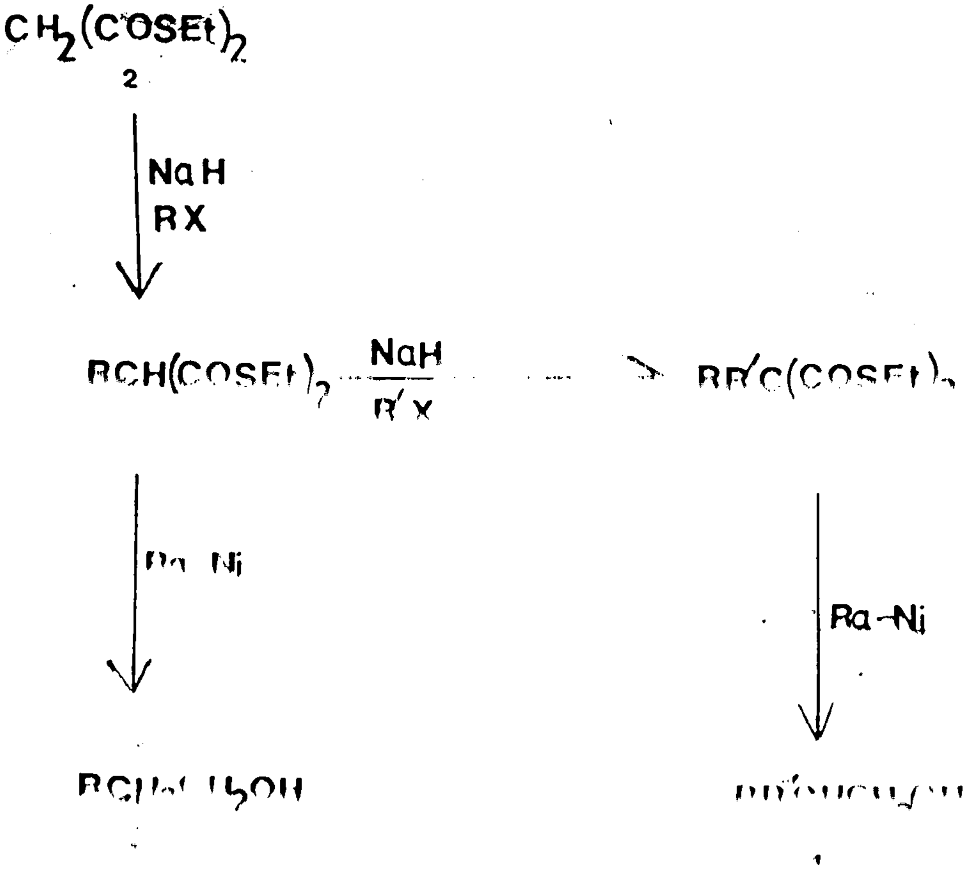
$CH_3CH_2S\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}SCH_2CH_3$

S,S'-Diethyl dithiomalonate (2) was first reported by Purvis and coworkers (13) in 1910, by the reaction of sodium ethylmercaptide with malonyl dichloride. Scheithauer and Mayer (14) prepared the same compound in two steps by reacting malononitrile with ethylmercaptan and hydrogen chloride followed by hydrolysis. An improved procedure for making S,S'-diethyl dithiomalonate (2) has recently been developed (12). The procedure makes use of the reaction between ethanethiol and malonyl dichloride and gives an excellent yield of the product.

Liu and Lai (12) succeeded in alkylating S,S'-diethyl dithiomalonate with a variety of alkyl halides, using sodium hydride in 1,2-dimethoxyethane. They also examined the reduction of the resulting 1,3-dithiol diesters with Raney nickel catalyst. In all cases, the alcohols of types 3 or 4, resulting from the removal of one thiolester group with the simultaneous reduction of the other were produced in excellent yields. As illustrated in Scheme I, the overall transformation can be considered as the replacement of one or two β-protons of ethyl alcohol by electrophiles, using S,S'-diethyl dithiomalonate (2) as an ethanol carbanion equivalent.

The use of S,S'-diethyl dithiomalonate (2) as a convenient source of ethanol carbanion equivalent has a considerable potential in organic syntheses. One

SCHEME I


CH2(COSEt)2
2
NaH
RX
RCH(COSEt)2
NaH
R'X
RR'C(COSEt)2
Ra-Ni
Ra-Ni
RCH(CH2OH)2
RR'C(CH2OH)2

interesting application is in its use as a Michael donor to facilitate the preparation of 1,5-ketols and 5-hydroxyesters, versatile synthetic intermediates which are particularly useful for the construction of six-membered carbocyclic and heterocyclic systems (15,16). The Michael reaction of S,S'-diethyl dithiomalonate (**2**) has received very limited attention. Its addition to ethyl acrylate and acrylonitrile was briefly explored (14), using sodium methoxide in methanol. Due to the inadequacy of the reaction conditions, the yields of the resulting 1,4-adducts were low. In addition, both the mono- and bis-adducts were formed indiscriminately in approximately equal amounts.

We have undertaken an extensive study of the Michael reaction of S,S'-diethyl dithiomalonate (**2**) as well as the reduction of the addition products with Raney nickel. The studies which are described in the first part of this thesis cumulate in the development of a new and convenient method for the preparation of 1,5-ketols and 5-hydroxyesters.

RESULTS AND DISCUSSION

S,S'-Diethyl dithiomalonate (**2**) used in the present studies was prepared by a slight modification of the procedure reported by Liu and Lai (12). In this modification, pyridine was included in the reaction of malonyl dichloride with ethanethiol. The inclusion of pyridine in the reaction was found to reduce the reaction time from the 16 hr required by the previous workers to 30 min. In addition, the modification allowed the preparation of S,S'-diethyl dithiomalonate (**2**) in quantitative yield.

In our initial attempts to induce the Michael reaction of S,S'-diethyl dithiomalonate (**2**) with a number of α,β-unsaturated carbonyl compounds, the use of the sodium and lithium salts of S,S'-diethyl dithiomalonate, generated <u>in situ</u> using sodium hydride and lithium tert-butoxide, was found to be completely ineffective. In all cases the starting materials were recovered. The failure of this procedure could be attributed to the unfavourable reversible nature of the reaction. Generally in Michael reactions in which the Michael donor can also serve as a good leaving group, the rate limiting step in which the new carbon-carbon bond is formed is reversible. The position of the equilibrium depends to a large extent on the stability of the intermediate enolate ion (15). The protonation of the enolate ion could, in principle, shift the equilibrium to the side of product formation, provided the deprotonation of the product, which could reverse the reaction, is sufficiently slow. Consequently, a likely solution to the problem encountered in the reaction of the sodium and lithium salts of S,S'-diethyl dithiomalonate with Michael acceptors, would be to carry out the reaction in the presence of a suitable proton source.

The use of an alkoxide in the presence of its conjugate acid (i.e. the corresponding alcohol) was considered. However, this combination was quickly ruled out, in view of the unfavourable results obtained in a similar study by Scheithauer and Mayer (14). In their work they used sodium methoxide in methanol to induce the Michael addition of S,S'-diethyl dithiomalonate (**2**) to acrylonitrile and ethyl acrylate. However, they obtained poor yields of the expected 1,4-adducts. A second possibility considered was the use of a mercaptide ion in the presence of the mercaptan. Unfortunately, because of the known ability of mercaptide to undergo facile 1,4-addition reactions with α,β-unsaturated carbonyl compounds, its use in the present studies would be particularly inappropriate.

The third possibility was to carry out the reaction in an aprotic solvent using a tertiary amine as base. This consideration was based on the mechanistic scheme shown in Scheme II, in conjunction with the following reasons: First, tertiary amines are sufficiently basic to deprotonate S,S'-diethyl dithiomalonate (**2**)[1] and therefore, in principle, should produce a reasonable concentration of the required anion **2a**. Secondly, the conjugate acid of the tertiary amine so generated is far more acidic (pK_a ~10) than a ketone (pK_a ~20) and consequently it can conveniently serve as an excellent proton source to trap the intermediate enolate ion **6**. Thirdly, the deprotonation of the ketonic product **7** which will also induce the retro-Michael process would not readily occur with the rather weak base such as a tertiary amine.

These predictions were found to be valid. The use of the tertiary amine, 1,4-diazabicyclo[2.2.2]octane (DABCO), was found to bring about a smooth reaction between S,S'-diethyl dithiomalonate (**2**) and a variety of α,β-unsaturated carbonyl compounds. In addition to DABCO,

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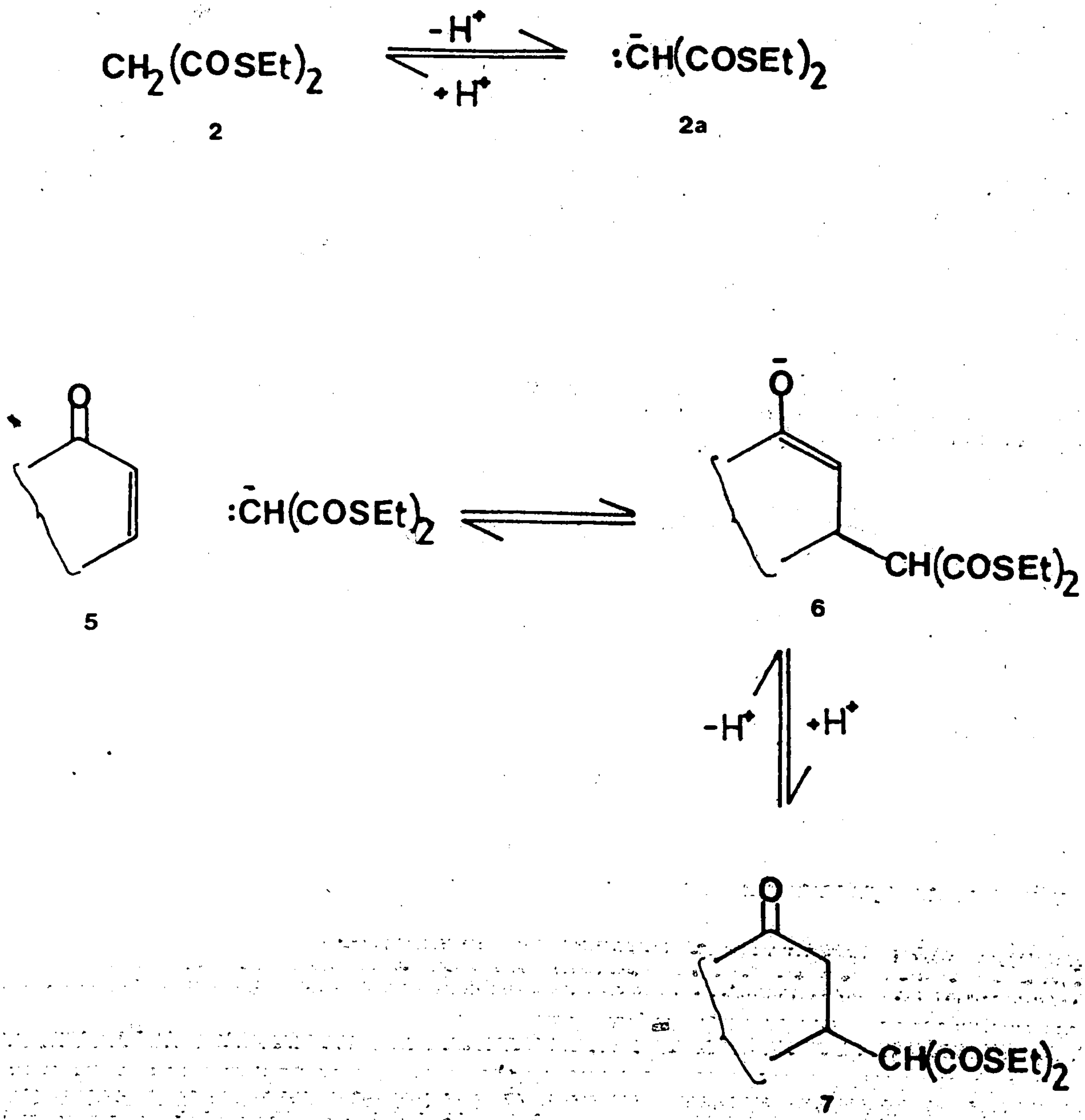
[1] Although the acidity of 2 remains to be ascertained, the closely related oxygen analogue is known to have a pK_a value of ~13.

SCHEME II


CH2(COSEt)2
-H+
+H+
:C̄H(COSEt)2
2
2a
:C̄H(COSEt)2
5
Ō
CH(COSEt)2
6
-H+
+H+
O
CH(COSEt)2
7

other tertiary amines including triethylamine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were also examined. Triethylamine was found to be ineffective. DBU and DBN, although they did induce the Michael reaction, were not as efficient as DABCO.

In principle, the Michael addition of **2** to an α,β-unsaturated carbonyl compound should require only a catalytic amount of base. In practice, however, it was found necessary to use one equivalent of DABCO with respect to S,S'-diethyl dithiomalonate (**2**). Lesser quantities resulted in incomplete reactions even after prolonged reaction times. Several solvent systems were examined. Benzene and 1,2-dimethoxyethane were found to be the most satisfactory.

As a typical example, S,S'-diethyl dithiomalonate (**2**) reacted smoothly with 2-cyclohexene-1-one in benzene at room temperature in the presence of DABCO. After 48 hr the expected 1,4-adduct **8** (Table 1) was obtained in greater than 90% yield. It was found that the rate of the reaction could be enhanced, as expected, by increasing the reaction temperature. However, the yield of the product was inferior. The ir spectrum of the adduct **8** showed absorption bands at 1660 and 1690 cm^{-1}, attributed to the thiolesters, and at 1700 cm^{-1} due to the ketone

TABLE I. Michael addition of S,S'-Diethyl dithiomalonate (2) to α,β-unsaturated carbonyl compounds and reduction of adducts with Raney nickel.

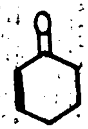
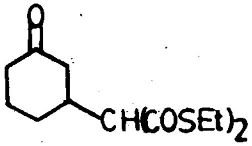
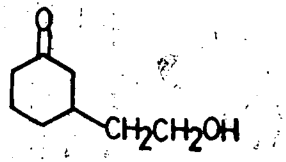
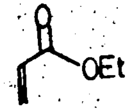
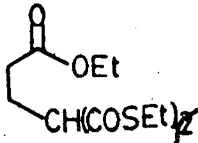
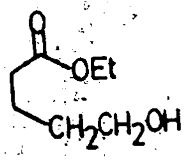
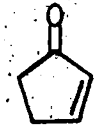
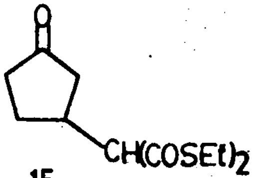
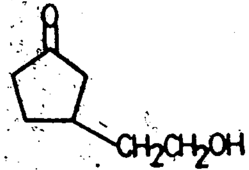
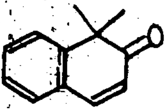
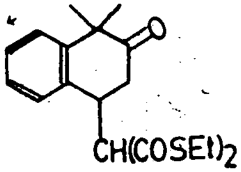
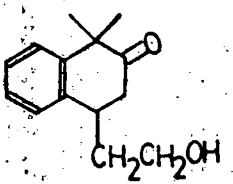
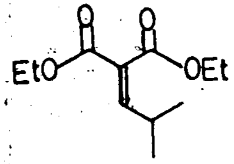
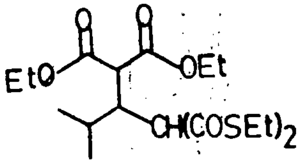
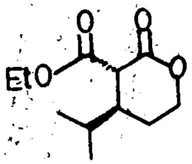
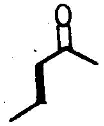
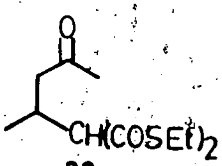
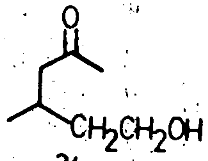
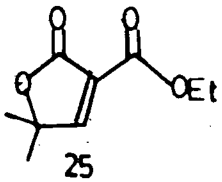
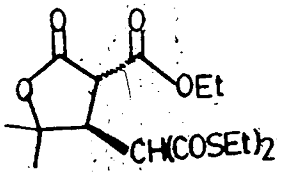
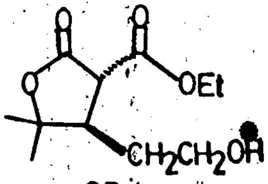
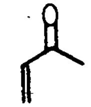
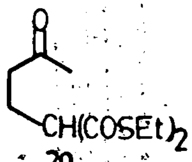
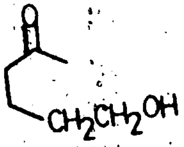
	Addition				Reduction		
Entry	α,β-unsaturated ketone (ester)	Time (hr)	Product	Yield %	Time (hr)	Product	Yield %
1		48	 8	93	1	 9	80
2		48	 13	93	4	 14	72
3		18	 15	95	1	 16	79
4	 17	24	 18	87	1	 19	86

TABLE I. (Cont'd.)

	Addition					Reduction	
Entry	α,β-unsaturated ketone (ester)	Time (hr)	Product	Yield %	Time (hr)	Product	Yield %
5	 20	5	 21	95	1	 22	70
6		24	 23	87	1	 24	79
7	 25	1	 26	100	0.5	 27	75
8		48[a]	 29	82	1	 30	86

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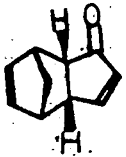
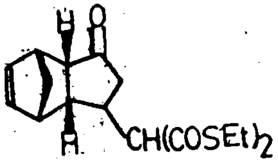
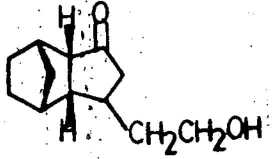
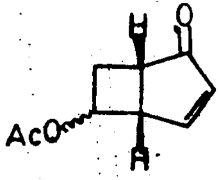
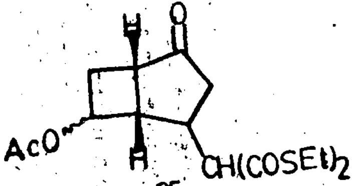
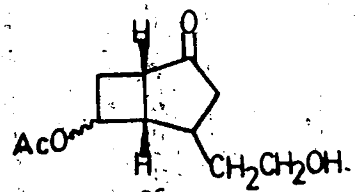
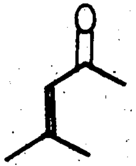
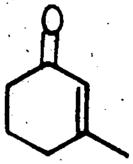
[a] This reaction was carried out -30°C. All other reactions were carried out at room temperature.

TABLE I. (Cont'd.)

Entry	α,β-unsaturated ketone (ester)	Addition Time (hr)	Addition Product	Addition Yield %	Reduction Time (hr)	Reduction Product	Reduction Yield %
9	 31	10	 32	100	3	 33	93
10	 34	48	 35	77	1	 36	95
11	 37	NR^b					
12		NR^b					

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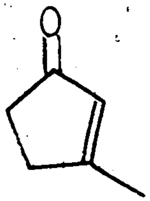
^{b}These compounds did not react with S,S'-diethyl dithiomalonate.

TABLE 1. (Cont'd.)

		Addition			Reduction		
Entry	α,β-unsaturated ketone (ester)	Time (hr)	Product	Yield %	Time (hr)	Product	Yield %
13		NR[b]					

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[b] This compound did not react with S,S'-diethyl dithiomalonate.

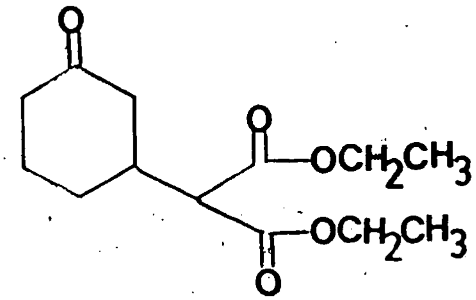
carbonyl. The nmr spectrum showed that the two thiolester groups were magnetically nonequivalent. This was evident from the appearance of triplets at δ1.28 and 1.27 and quartets at δ2.92 and 2.94 with a coupling constant of 8 Hz. These signals were assigned to the thiolester groups. The methine proton of the dithiomalonate moiety appeared as a doublet at δ3.70 with a coupling constant of 10 Hz. Both the mass spectrum and elemental analysis were in agreement with the molecular formula of $C_{13}H_{20}O_3S_2$.

The above conditions for the reaction of S,S'-diethyl dithiomalonate (2) with 2-cyclohexen-1-one were found to be generally applicable to all the α,β-unsaturated carbonyl compounds studied. The details of the individual reactions will be discussed later on in this thesis.

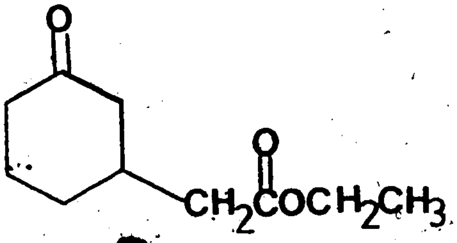
Having succeeded in the development of a general method for the rapid incorporation of a dithiomalonate unit into the β-position of an α,β-unsaturated carbonyl compound, we turned our attention to the study of the Raney nickel reduction of the resulting adducts. It was expected, based on the previous work by Liu and Lai (12), that Raney nickel reduction of the dithiomalonate adducts would lead to the removal of one thiolester group with the concomitant reduction of the other to the alcohol level. Initially, attempts were made to achieve this transformation using standard W-2 Raney nickel (11).

However, it was soon realized that this reagent was not satisfactory. Apart from the desired product which was obtained in low yield, by-products were also detected. For example, when the Michael adduct **8** (Table 1) was treated with the standard W-2 Raney nickel in benzene at room temperature, three products **9** (Table 1), **10** and **11** were obtained in a total of 65% yield and in a ratio of 1:1.5:1.

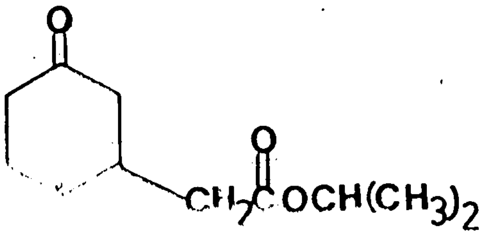
The production of compound **10** can be attributed to a complete transesterification of the dithiolester with ethanol. Such a transesterification is not unexpected in view of the large quantities of ethanol and sodium hydroxide used in the preparation of W-2 Raney nickel. Even though the preparation of W-2 Raney nickel involves a sequential wash with water until neutral, ethanol to remove water, and benzene to remove ethanol, it is conceivable that some quantity of base and ethanol could still be trapped in the catalyst. The presence of these trapped chemicals could bring about the transesterification and, once such a transesterification occurs, the ketodiester **10** produced is inert to Raney nickel. The keto monoester **11** may be arising from a monotransesterification process followed by a dealkylthiocarbonylation reaction or vice versa



10



11



12

In order to circumvent this problem it was intended to replace the ethanol with a more bulky alcohol in the preparation of the W-2 Raney nickel so as to suppress the transesterification process. Tertiary-butyl alcohol was the first to be considered. However it was found to be inappropriate due to its high freezing point. As a result isopropyl alcohol was used. When adduct **8** was treated with the Raney nickel so prepared, considerable improvement in the reaction was observed. The yield of the desired product **9** was increased by 30% and the di-transesterification product was not detected. However, the reaction still produced a small quantity of byproduct **12** resulting from mono-transesterification with isopropyl alcohol. In order to further improve the reaction conditions, it was deemed necessary to ascertain that the Raney nickel was free of hydroxide ions. To effect this aqueous acetic acid was included in the washing process. Thus, after the Raney nickel was formed according to the known procedure, it was washed sequentially with water, aqueous acetic acid, water, isopropyl alcohol, and benzene, instead of the normal water, ethanol, and benzene combination. This modified W-2 Raney nickel proved to be very effective and completely eliminated the transesterification [illegible]

When the Michael adduct 8 was treated with an excess (~0.04 mL/mg of substrate) of this modified W-2 Raney nickel at room temperature in benzene, an 80% yield of the 5-hydroxyketone 9 was obtained. The structure of this compound was apparent from the spectral data. The ir spectrum showed only the ketone carbonyl and the alcohol absorption bands at 1710 and 3420 cm^{-1} respectively. The nmr spectrum displayed the characteristic triplet at δ3.50 with a coupling constant of 9 Hz, attributed to the methylene protons adjacent to the hydroxyl group. The mass spectrum and elemental analysis were in complete agreement with the assigned structure. In all the subsequent work this modified W-2 Raney nickel was used and was found to be highly satisfactory in achieving the desired results.

To study the generality of the Michael reaction of S,S'-diethyl dithiomalonate (2), a variety of α,β-unsaturated carbonyl compounds were used. The compounds chosen included both ketones and esters with different degrees of substitution at the α- and β-carbon centres. We have also successfully examined the reduction of the adducts to the alcohol level with the modified W-2 Raney nickel. The results of these studies are compiled in Table 1. The reactions are discussed individually in some detail.

S,S'-Diethyl dithiomalonate (2) reacted with ethyl acrylate in 1,2-dimethoxyethane at room temperature in the presence of DABCO to afford the expected Michael adduct **13** in 93% yield. The ir spectrum of the adduct showed diagnostic absorption bands at 1730 (ester carbonyl), 1665 and 1695 cm^{-1} (thiolesters). The nmr spectrum showed a triplet (J = 8 Hz) at δ1.28, which integrated for a total of nine protons. This signal was attributed to a total of three methyl groups of the thiolester and ester moieties. However, due to the higher electronegativity of oxygen compared to sulfur, the methylene protons of the ethyl ester group appeared as a quartet at δ4.12 and with a coupling constant of 8 Hz, while the methylene protons of both thiol ester groups appeared at a much higher field of δ2.90 with the same multiplicity and coupling constant. The methine proton of the dithiomalonate group appeared as a triplet at δ3.90 and with a coupling constant of 10 Hz. The mass spectrum lacked a molecular ion peak but showed two prominent peaks at 231.0695 and 247.0467. These peaks were attributed to the loss of SCH_2CH_3 and OCH_2CH_3 respectively from the parent ion. Elemental analysis confirmed the molecular formula of $C_{12}H_{20}O_4S_2$. Raney nickel reduction of the Michael adduct **13**, occurred smoothly at room temperature to give the δ-hydroxyester **14** in 72% yield. The product showed the characteristic ester and alcohol bands at 1730 and 3420 cm^{-1}, respectively. In the nmr spectrum a three-proton triplet at δ1.24 and a two-proton quartet at δ4.10, each with a coupling constant of 8 Hz, indicated the presence of the ethyl ester group. The two methylene protons adjacent to the hydroxyl group appeared as a triplet, with a coupling constant of 9 Hz at δ3.66 while the hydroxyl proton was a broad singlet at δ2.80. The mass spectrum did not show a molecular ion peak, but the prominent peak at 101.0601 was attributed to the loss of an OCH_2CH_3 unit. Elemental analysis confirmed the molecular formula of $C_7H_{14}O_3$.

The reaction of dithiomalonate **2** with 2-cyclopenten-1-one was carried out in benzene and gave the expected adduct **15** in 95% yield. This compound showed two sets of signals for the two thiolester groups; two methyl triplets at δ1.28 and 1.30 and two methylene quartets at δ2.96 and 2.98 each with a coupling constant of 8 Hz. The methine proton of the dithiomalonate group appeared as a doublet at δ3.72 (J = 10 Hz). In the ir spectrum, the absorption bands at 1735, 1690 and 1660 cm^{-1} were indicative of the presence of both five-membered ketone and thiolester carbonyls. When the adduct **15** was treated with Raney nickel, a 79% yield of the ketoalcohol **16** was obtained. This compound showed absorption bands at 3420 (alcohol) and 1730 cm^{-1} (ketone carbonyl) in the ir spectrum. In the nmr spectrum the methylene protons adjacent to the hydroxyl group appeared as a triplet at δ3.24 with a coupling constant of 9 Hz, while the hydroxyl proton appeared as a singlet at δ2.20. The structural assignment was further confirmed by mass spectral and elemental analyses. The former showed a molecular ion peak at 128.0838 in agreement with the required molecular formula of $C_7H_{12}O_2$.

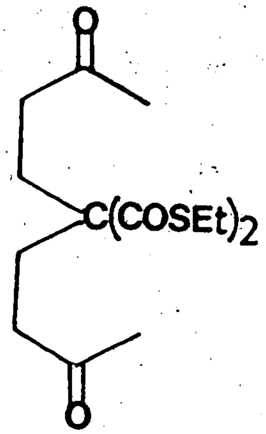
The Michael addition of S,S'-diethyl dithiomalonate (**2**) to 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (**17**) gave the desired adduct **18** in 87% yield. The ir spectrum displayed the characteristic ketone carbonyl band at 1710 cm^{-1} and the thiolester bands at 1660 and 1685 cm^{-1}. The magnetic nonequivalence of the two thioethyl groups in the molecule was evident from the appearance, in the nmr spectrum, of methyl triplets (J = 8 Hz each) at δ1.06 and 1.30 and methylene quartets at δ3.00 and 3.08 each with a coupling constant of 8 Hz. The gem-dimethyl group appeared as singlets at δ1.44 and 1.54. A one-proton doublet at δ3.60 with a coupling constant of 10 Hz was assigned to the methine proton of the dithiomalonate group. The nmr spectrum also indicated the presence of four aromatic protons which appeared in the δ7.1-7.4 region. Raney nickel reduction of the adduct **18** occurred readily at room temperature. The product **19** which was obtained in 86% yield, showed a broad band at 3400 cm^{-1} for a hydroxy group and a characteristic ketone absorption band at 1710 cm^{-1} in the ir spectrum. In agreement with the structural assignment, the nmr spectrum showed two sharp methyl singlets at δ1.40 and 1.50, and a multiplet at δ7.20 for the aromatic protons. The methylene protons adjacent to the hydroxyl group appeared as a triplet with a coupling constant of 8 Hz at δ3.24, while the hydroxy proton was observed at δ2.90 as a singlet.

S,S'-Diethyl dithiomalonate (**2**) added to ethyl 2-carboethoxy-4-methyl-2-pentenoate (**20**) in the presence of DABCO in 1,2-dimethoxyethane to give a 95% yield of the expected adduct **21**. The structure of the adduct was evident from the spectral analyses. In the ir spectrum, the two bands at 1660 and 1690 cm^{-1} were assigned to the thiolesters while the band at 1735 cm^{-1} was assigned to the ester carbonyl. In addition to two methyl doublets ($J = 7$ Hz each) at δ0.85 and 0.98, the nmr spectrum showed two six-proton triplets ($J = 8$ Hz each), one at δ1.22 and the other at δ1.30. These signals can be attributed to a total of four methyls of both the malonate and dithiomalonate groups. Two doublets, each with a coupling constant of 10 Hz, were also observed in the nmr spectrum at δ3.58 and 3.50. These two signals were consistent with the presence of two methine protons of the malonate and dithiomalonate groups. Although the molecular ion peak was not observed in the mass spectrum, the presence of a prominent peak at 345.1370 indicated the loss of an SCH_2CH_3 unit. Elemental analysis confirmed the molecular formula of $C_{18}H_{30}S_2O_6$. When adduct **21** was reduced with Raney nickel, it afforded a single compound which did not show the expected alcohol absorption band in the ir spectrum. The only diagnostic bands were at 1735 and 1750 cm^{-1} indicative of an ester and a lactone carbonyl moiety. Further spectra analyses confirmed that the compound was not the expected alcohol but the lactone **22**. In the nmr spectrum a three-proton triplet at $\delta 1.20$ and a two-proton quartet at 4.20, each with a coupling constant of 8 Hz, were attributed to the ethyl ester. Furthermore, the compound showed a triplet at $\delta 3.85$ ($J = 8$ Hz), which can be assigned to the methylene bearing the oxygen atom. These spectral data also strongly indicated that the compound was a single stereoisomer. The fact that the methine proton adjacent to the two carbonyls appeared as a doublet at $\delta 3.40$ and with the large coupling constant of 8 Hz further suggested that the compound was the trans isomer as shown.

The reaction of the dithiomalonate **2** with 3-penten-2-one using DABCO occurred readily in benzene to give the adduct **23** in 87% yield. The ir spectrum exhibited absorption bands at 1710 (ketone carbonyl), 1658 and 1680 cm^{-1} (thiolesters). In the nmr spectrum, a three-proton singlet at δ2.13 and a three-proton doublet at δ1.00 (J = 8 Hz) were attributed to the methyls attached to the ketone carbonyl and the carbon bearing the dithiomalonate group, respectively. A six-proton triplet at δ1.27 and a four proton quartet at δ2.90, each with a coupling constant of 8 Hz, were assigned to the methyl and methylene protons, respectively, of the thiolester groups. The methine proton of the dithiomalonate group appeared as a doublet at δ3.80 (J = 10 Hz). The mass spectrum did not show a molecular ion peak but rather a prominent peak at 153.0552 due to the loss of two SCH_2CH_3 units. Elemental analysis further confirmed the molecular formula of $C_{12}H_{20}O_3S_2$. Raney nickel reduction of adduct **23** afforded the 5-hydroxyketone **24** in 79% yield. The product exhibited the diagnostic ketone carbonyl band at 1710 cm^{-1} and also the band at 3420 cm^{-1} for the hydroxyl group. The nmr spectrum was in agreement with the proposed structure. A three-proton singlet at δ2.40 was due to the methyl attached to the carbonyl while the other methyl group appeared as a doublet centered at δ1.00 and with a coupling constant of 8 Hz. A doublet at δ2.24 (J = 6 Hz) which integrated for two protons was readily assigned to the methylene protons alpha to the carbonyl. The methylene protons adjacent to the hydroxyl group appeared as a triplet at δ3.25 with a coupling constant of 9 Hz. The mass spectral and elemental analyses were in complete agreement with the molecular formula of $C_7H_{14}O_2$.

The dithiomalonate **2** reacted with 3-carboethoxy-5,5-dimethyl-2(5H)-furanone (**25**) in 1,2-dimethoxyethane at room temperature to give the expected Michael adduct **26** in a quantitative yield. The ir spectrum of the adduct showed diagnostic absorption bands at 1730 (ester carbonyl), 1780 (lactone carbonyl), 1660 and 1680 cm^{-1} (thiolesters). In addition to the gem-dimethyl group which appeared as a singlet at δ1.48, the nmr spectrum displayed a six-proton triplet at δ1.26 and a three-proton triplet at δ1.32, both with a coupling constant of 8 Hz. These signals were attributed to the methyls of the dithiomalonate group and the methyl of the ester moiety, respectively. The remaining signals were also characteristic of the compound. The methylene protons of the thiolester groups appeared as a quartet (J = 8 Hz) at δ2.94 while those of the ester appeared at a much lower field of δ3.66 with the same multiplicity and coupling constant. The methine proton of the dithiomalonate unit appeared as a doublet at δ3.40 (J = 10 Hz). The doublet at δ3.90, having a coupling constant of 6 Hz, was readily assigned to the proton on the carbon flanked by two carbonyl groups. These spectral data further indicated the presence of a single stereoisomer. However, the stereochemical assignment could not be made unambiguously on the basis of the coupling constant (6 Hz) alone. In assigning the tentative stereochemistry, it was also considered that compound **26** can readily undergo isomerization due to the presence of the acidic proton and, of the two possible stereoisomers, the <u>trans</u> form should be thermodynamically more stable. Reduction of adduct **26** with the modified W-2 Raney nickel gave the expected alcohol **27** in 75% yield. All the spectral data were consistent with the structure. The ir spectrum showed characteristic bands at 1735 (ester carbonyl), 1780 (lactone carbonyl) and 3500 cm^{-1} (alcohol). In the nmr spectrum a two-proton quartet at $\delta 3.65$ and a three-proton triplet at $\delta 1.30$, each with a coupling constant of 8 Hz, were indicative of the presence of the carbethoxy group. The <u>gem</u>-dimethyl protons appeared as a singlet at $\delta 1.46$, while the two-proton multiplet at $\delta 3.16$ was assigned to the methylene adjacent to the hydroxyl group. The hydrogen on the carbon flanked by two carbonyl groups appeared as a doublet at $\delta 3.85$ with a coupling constant of 8 Hz. The assigned stereochemistry follows from that of the precursor **26**.

The reaction of S,S'-diethyl dithiomalonate (**2**) with methyl vinyl ketone was the only case where the production of a bis-adduct **28** was encountered. When the reaction of methyl vinyl ketone with one equivalent of S,S'-diethyl dithiomalonate (**2**) and one equivalent of DABCO was performed in 1,2-dimethoxyethane at room temperature, less than 10% of the mono-adduct **29** was obtained. The major product was the bis-adduct **28** which was formed in 80% yield as a white solid. An increase in the number of equivalents of S,S'-diethyl dithiomalonate (**2**) did not improve the yield of the required mono-adduct. However, when the temperature was lowered to 0°C, one equivalent of S,S'-diethyl dithiomalonate (**2**) gave 33% yield of the mono-adduct and 56% yield of the bis-adduct. It was found that at −30°C the mono-adduct could be obtained in 82% yield. Even at this temperature approximately 10% of the bis-adduct was produced. Further lowering of temperature failed to improve the yield of the mono-adduct. In fact, at −78°C no reaction occurred between dithiomalonate **2** and methyl vinyl ketone. The ir spectrum of the monoadduct **29** showed the ketone carbonyl band at 1710 cm^{-1} while the two bands at 1660 and 1685 cm^{-1} were assigned to the thiolesters. The nmr spectrum displayed a six-proton triplet at δ1.12 and a four-proton quartet at δ2.60 each with a coupling constant of 8 Hz. These signals were



28.

attributed to the methyls and methylenes, respectively, of the thiolesters. In addition, a three-proton singlet at δ1.84 was assigned to the methyl attached to the carbonyl group. The methine proton of the dithiomalonate group appeared as a triplet (J = 10 Hz) at δ3.40. The mass spectrum of the adduct **29** did not show a molecular ion peak but the prominent peak at 139.0394 which was readily assigned to the loss of $C_4H_{11}S_2$ from the molecular ion. Elemental analysis confirmed the molecular formula of $C_{11}H_{18}O_3S_2$. The mono-adduct **29** was readily reduced by Raney nickel to give an 86% yield of the expected ketol **30**. The structure of the ketol was confirmed spectroscopically. The two bands at 1710 and 3410 cm^{-1} in the ir spectrum were indicative of a ketone carbonyl and an alcohol, respectively. In the nmr spectrum, the signal at δ1.90, which appeared as a three-proton singlet, was assigned to the methyl attached to the carbonyl group. The methylene protons α to the carbonyl appeared as a triplet at δ2.30 with a coupling constant of 6 Hz, while the methylene adjacent to the hydroxyl group was a multiplet at δ3.70. The mass spectrum lacked a molecular ion peak, but the prominent peak at 100.0879 was indicative of the loss of the elements of water from the molecular ion. The elemental analysis [illegible] the molecular formula of [illegible]

The reaction of dithiomalonate **2** with cis-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**31**) was carried out in 1,2-dimethoxyethane and gave the expected 1,4-adduct **32** in a quantitative yield. In the ir spectrum, the absorption bands at 1730, 1660 and 1690 cm^{-1} were indicative of the presence of both five-membered ketone and thiolester carbonyls. The compound showed two sets of signals for the two thiolester groups in the nmr spectrum; two methyl triplets at δ1.24 and δ1.30 and two methylene quartets at δ2.96 and 2.298, each with a coupling constant of 8 Hz. The methine proton of the dithiomalonate group appeared as a doublet (J = 10 Hz) centered at δ3.82. The two vinyl protons appeared at δ6.16 and 6.24, each as a doublet of doublets (J = 2 Hz, J' = 4 Hz). The nmr spectrum strongly indicated the presence of a single stereoisomer. The assigned stereochemistry **32** was based on the consideration that the addition should occur from the less hindered exo side of the molecule. Raney nickel reduction of adduct 32 occurred smoothly at room temperature to afford a 93% yield of the ketol 33. The ir spectrum showed a ketone carbonyl band at 1720 cm^{-1} and an alcohol band at 3400 cm^{-1}. The nmr spectrum of the product showed a one proton broad singlet for the hydroxyl group at δ2.50 and a triplet at δ3.20 (J = 8 Hz) for the methylene protons [illegible] to the hydroxyl group. The absence of vinylic protons clearly indicated that the olefinic double bond was also reduced during the Raney nickel treatment. Attempts were made to preserve the double bond by using partially deactivated Raney nickel, obtained by boiling the Raney nickel in acetone. However, this was found to be unsatisfactory and resulted in the formation of a complex mixture.

S,S'-Diethyl dithiomalonate (**2**) was reacted with a 1:1 mixture of 6-acetoxy-_cis_-bicyclo[3.2.0]hept-3-en-2-one (**34**) epimeric at the carbon bearing the acetoxy group. The reaction was carried out with DABCO in 1,2-dimethoxyethane and at room temperature to give a 77% yield of two inseparable products. In the ir spectrum the ketone carbonyl and the acetoxy carbonyl appeared as a broad band at 1730 cm^{-1} while the thiolesters appeared as two bands at 1660 and 1690 cm^{-1}. The nmr spectrum showed two triplets at δ1.26 and 1.29 and two quartets at δ2.96 and 2.90 each with a coupling constant of 8 Hz. These signals were attributed to the two thiolester groups. The methine proton of the dithiomalonate group appeared as a doublet at δ3.76 (J = 10 Hz). In addition, the nmr spectrum displayed two singlets at δ2.06 and 2.12 in a 1:1 ratio for a total of three hydrogen atoms. These signals were attributed to the methyl of the acetoxy moiety. The [illegible] data clearly indicated that the product was [illegible] two stereoisomers. Since the starting material was a 1:1 mixture of two epimers, the production of two stereoisomers could only have resulted from a completely stereospecific addition of the incoming dithiomalonate group. The stereochemistry of the newly created asymetric centre was tentatively assigned based on the expected addition of the incoming group from the less hindered exo side of the molecule. Adduct **35** underwent smooth Raney nickel reduction to give the alcohol **36** in 95% yield. The spectral data was consistent with the structure. The ir spectrum showed characteristic peaks at 1725 (carbonyl) and 3400 cm^{-1} (alcohol). In the nmr spectrum the hydroxyl proton appeared as a broad singlet at δ4.15, while the methylene protons adjacent to the hydroxyl group appeared as a multiplet at δ3.60. Again two singlets were observed at δ2.12 and 2.06 for a total of three protons of the acetoxy group indicating the presence of two stereoisomers. Both the mass spectral and elemental analyses were in agreement with the molecular formula of $C_{11}H_{16}O_4$.

The reaction of S,S'-diethyl dithiomalonate (**2**) with Michael acceptors in which the β-carbon was fully substituted was also examined. However, under a variety of conditions S,S'-diethyl dithiomalonate (**2**) failed to react with mesityl oxide (**37**), 3-methyl-2-cyclohexen-1-one and 3-methyl-2-cyclopenten-1-one, even after prolonged treatment at elevated temperatures using different bases. In all cases the starting materials were recovered. These results indicated that the current procedure is not applicable to α,β-unsaturated carbonyl compounds fully substituted at the β-carbon.

The results presented above show that S,S'-diethyl dithiomalonate readily undergoes Michael reactions with α,β-unsaturated carbonyl compounds other than the ones fully substituted at the β-carbon. The reaction, which is highly facilitated by the use of DABCO as a base, could be carried out under mild conditions and gives excellent yields of adducts. These adducts are easily reduced with Raney nickel to the corresponding ethanol derivatives. The two-step operation provides a new and convenient method for the preparation of 5-hydroxyesters and 1,5 ketols, using S,S'-diethyl dithiomalonate (2) as an ethanol carbanion equivalent.

EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer. Unless otherwise stated, ir samples were run as thin films. Proton nuclear magnetic resonance (nmr) spectra were recorded on a Varian HA-100, HA-100/Digilab, Bruker WP-80 or Bruker WH-200 spectrometer and, except where otherwise stated, were obtained on solutions in deuterated chloroform with tetramethylsilane as internal reference. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad. Mass spectra (ms) were recorded using A.E.I. model MS9, MS12 or MS50 mass spectrometers. Concentrations of solvent systems used in column chromatography are given by volumes, e.g. 10% ethyl acetate in hexane means 10 parts ethyl acetate by volume to 90 parts hexane by volume.

Materials

Ether, benzene and 1,2-dimethoxyethane used for reactions were freshly distilled from lithium aluminum hydride. Pyridine was distilled from barium oxide and stored over potassium hydroxide pellets. Nitrogen and argon were passed through a purification train of Fieser's solution, concentrated sulfuric acid and potassium hydroxide pellets. Silica gel, 0.040-0.063 mm particle size, 230-400 mesh ASTM, was used as adsorbent for flash chromatography (17) and silica gel, 60-120 mesh, was used as adsorbent for column chromatography. Thin-layer chromatography was carried out using Merck silica gel G (type 60). Unless otherwise stated, anhydrous magnesium sulfate was used for drying organic solutions. Commercially available methyl vinyl ketone, 2-cyclohexen-1-one, ethyl acrylate, 3-penten-2-one and 2-cyclopenten-1-one were distilled before use. Ethyl 2-carboethoxy-4-methyl-2-pentenoate (**20**) was prepared by the method of Cope and coworkers (18). 3-Carboethoxy-5,5-dimethyl-2(5H)-furanone (**25**) was made according to the described procedure (19). 6-Acetoxy-cis-bicyclo[3.2.0]hept-3-en-2-one was previously prepared by Bulat (20). 1,1-Dimethyl-2-oxo-1,2-dihydronaphthalene (**17**) was made by the method of Marvell and Stephenson (21) and cis-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**31**) was prepared by the method of Alder and Flock (22). Malonyl dichloride was prepared by reacting malonic acid with two equivalents of thionyl chloride (23).

Modified W-2 Raney Nickel

A solution of sodium hydroxide (190 g) in distilled water (750 mL) was cooled in an ice bath to 10°C. Nickel-aluminum alloy (150 g) was added slowly with stirring. During the addition, the temperature of the mixture was not allowed to rise above 25°C. After the addition, the mixture was allowed to warm up to room temperature and was stirred for 12 hr on a steam bath. The solvent was decanted and the residue washed with distilled water (2 × 500 mL), a solution of sodium hydroxide (25 g) in water (250 mL) was added. The mixture was stirred at room temperature for 15 min. After decanting the water, the residue was washed sequentially with distilled water (4 × 500 mL), 0.05 M aqueous acetic acid (4 × 500 mL), water (4 × 600 mL), isopropyl alcohol (3 × 200 mL) and benzene (3 × 200 mL).

S,S'-Diethyl dithiomalonate (**2**)

A solution of ethanethiol (52.56 mL, 0.71 mol) in ether (100 mL) was added dropwise to a solution of malonyl dichloride (40.00 g, 0.28 mol) in ether (100 mL) with stirring. A solution of pyridine (33.95 mL, 0.42 mol) in ether (50 mL) was then added slowly over a period of 10 min. The reaction mixture was stirred for an additional 15 min at room temperature. Most of the solvent was evaporated and the residue distilled under reduced pressure to afford the pure S,S'-diethyl dithiomalonate (**2**) (53 g; 100% yield): b.p. 100°C/2 torr; ir 1660 and 1680 cm^{-1} (thiolesters); nmr $\delta 1.24$ (t, 6H, J = 8 Hz, 2× $-COSCH_2C\mathbf{H}_3$), 2.92 (q, 4H, J = 8 Hz, 2× $-COSC\mathbf{H}_2CH_3$) and 3.70 (s, 2H, $-CH_2-$); ms M^+ 192.0277 (calcd. for $C_7H_{12}O_2S_2$: 192.0268); Anal. Calcd. for $C_7H_{12}O_2S_2$: C 43.74, H 6.30, S 33.30; Found: C 43.69, H 6.57, S 33.30.

Addition of **2** to Ethyl Acrylate

A solution of S,S'-diethyl dithiomalonate (**2**) (432 mg, 2.25 mmol), DABCO (253 mg, 2.25 mmol) and ethyl acrylate (150 mg, 1.5 mmol) in 1,2-dimethoxyethane (20 mL) was stirred at room temperature under an argon atmosphere for 48 hr. The resulting mixture was poured into 2N aqueous hydrochloric acid solution (50 mL) and extracted with dichloromethane (3 × 25 mL). The combined extract was dried, filtered and concentrated to give the crude product which was chromatographed on silica gel. Elution with a solution of 10% ethyl acetate in petroleum ether gave the pure adduct **13** (367 mg; 93% yield): ir 1730 (ester carbonyl), 1695 and 1665 cm^{-1} (thiolesters); nmr $\delta 1.28$ (t, 9H, J = 8 Hz, $OCH_2C\mathbf{H}_3$ and 2× $-COSCH_2C\mathbf{H}_3$), 3.90 (t, 1H, J = 10 Hz, $-COCHCO-$) and 4.12 (q, 2H, J = 8 Hz, $-OC\mathbf{H}_2CH_3$); ms m/e 247.0467 (M^+-45; calcd. for $C_{10}H_{15}O_3S_2$: 247.0464) and 231.0695 (M^+-61; calcd. for $C_{10}H_{15}O_4S$: 231.0692); Anal. Calcd. for $C_{12}H_{20}O_4S_2$: C 49.32, H 6.90, S 21.89; Found: C 49.61, H 7.00, S 22.04.

Reduction of the Adduct **13**

A solution of the adduct **13** (980 mg, 2.34 mmol) in benzene (10 mL) was added to a suspension of Raney nickel (6 mL, settled volume) in benzene. The mixture was stirred under an argon atmosphere at room temperature for 4 hr, and then filtered. The residue was washed thoroughly with benzene and the filtrate concentrated. Chromatography of the crude material on silica gel, eluting with 10% ethyl acetate in petroleum ether, afforded the hydroxy ester **14** (350 mg; 72% yield): ir 1730 (ester carbonyl) and 3420 cm^{-1} (alcohol); nmr δ1.24 (t, 3H, J = 8 Hz, $-CH_3$), 2.66 (t, 2H, J = 9 Hz, $-CH_2CH_2CO-$), 1.60 and 2.30 (m, 4H, $-CH_2CH_2-$), 2.80 (s, 1H, OH), 3.80 (t, 2H, J = 9 Hz, $-CH_2OH$) and 4.10 (q, 2H, J = 8 Hz, $-OCH_2CH_3$); ms m/e 101.0601 (M^{+}-45; calcd. for $C_5H_9O_2$: 101.0603). Anal. Calcd. for $C_7H_{14}O_3$: C 57.50, H 9.66; Found: C 57.41, H 9.45.

Addition of **2** to 2-Cyclopenten-1-one

A solution of S,S'-diethyl dithiomalonate (1.00 g, 5.00 mmol), DABCO (580 mg, 5.00 mmol) and 2-cyclopenten-1-one (630 mg, 770 mmol) in benzene (15 mL) was stirred at room temperature under an argon atmosphere for 18 hr. The mixture was poured into a 2N aqueous hydrochloric acid solution (50 mL) and extracted with dichloromethane (2 × 25 mL). The combined organic extract was dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with a solution of 10% ethyl acetate in petroleum ether gave the adduct **15** (130 mg, 95% yield): ir 1735 (ketone carbonyl), 1660 and 1690 cm [illegible] (thiolesters); nmr δ1.28 (t, 3H, J = 8 Hz, $-SCH_2CH_3$), 1.30 (t, 3H, J = 8 Hz, $-SCH_2CH_3$), 2.96 (q, 2H, J = 8 Hz, $-SCH_2CH_3$), 2.98 (q, 2H, J = 8 Hz, $-SCH_2CH_3$), 3.72 (d, 1H, J = 10 Hz, -COCHCO-); ms M^+ 274.0702 (calcd. for $C_{12}H_{18}O_3S_2$: 274.0698). Anal. Calcd. for $C_{12}H_{18}O_3S_2$: C 52.54, H 6.62, S 23.33; Found: C 52.59, H 6.62, S 23.51.

Reduction of the Adduct 15

To a suspension of Raney nickel (8 mL, settled volume) in benzene (10 mL) was added a solution of the adduct **15** (650 mg, 2.37 mmol) in benzene (10 mL). The mixture was stirred for 1 hr at room temperature under an argon atmosphere. It was then filtered and the residue washed with benzene (3 × 15 mL). The filtrate was concentrated and the crude material purified on a silica gel column. Elution with a 10% ethyl acetate in petroleum ether solution gave the pure ketol **16** (211 mg; 79% yield): ir 1730 (five-membered ketone carbonyl) and 3420 cm^{-1} (alcohol); nmr δ3.24 (t, 2H, J = 9 Hz, $-CH_2OH$), 2.20 (s, 1H, -OH) and 2.23 (m, 4H, $-CH_2COCH_2-$); ms M^+ 128.0841 (calcd. for $C_7H_{12}O_2$: 128.0838). Anal. Calcd. for $C_7H_{12}O_2$: C 65.58, H 9.44; Found: C 65.71, H 9.52.

Addition of **2** to 1,1-Dimethyl-2-oxo-1,2-dihydronaphthalene (**17**)

To a solution of DABCO (135 mg, 1.20 mmol) and S,S'-diethyl dithiomalonate (231 mg, 1.20 mmol) in 1,2-dimethoxyethane (10 mL) was added a solution of 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (**17**) (172 mg, 1.00 mmol) in 1,2-dimethoxyethane (5 mL). The mixture was stirred at room temperature under an argon atmosphere for 24 hr. The reaction mixture was poured into 2N aqueous hydrochloric acid solution (25 mL) and extracted with dichloromethane (2 × 15 mL). The organic extract was dried, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel. Elution with a 10% solution of ethyl acetate in petroleum ether gave the adduct **18** (348 mg; 87% yield): ir 1710 (ketone carbonyl), 1660 and 1685 cm^{-1} (thiolesters); nmr δ1.06 (t, 3H, J = 8 Hz, $-SCH_2CH_3$), 1.30 (t, 3H, J = 8 Hz, $-SCH_2CH_3$), 1.44 (s, 3H, $-CH_3$), 1.54 (s, 3H, $-CH_3$), 3.60 (d, 1H, J = 10 Hz, -COCHCO-), 3.00, 3.08 (both q, 2H each, J = 8 Hz each, 2× $-COSCH_2CH_3$) and 7.1-7.4 (m, 4H, aromatic protons); ms M$^+$ 364.1177 (calcd. for $C_{19}H_{24}O_3S_2$: 364.1168). Anal. Calcd. for $C_{19}H_{24}O_3S_2$: C 62.62, H 6.64, S 17.56; Found: C 62.48, H 6.54, S 17.61.

Reduction of the Adduct **18**

A solution of the adduct **18** (200 mg, 0.55 mmol) in benzene (10 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The mixture, after stirring at room temperature for 1 hr, was filtered, concentrated and purified by column chromatography on silica gel. Elution with a solution of 15% ethyl acetate in petroleum ether afforded the pure ketol **19** (103 mg; 86% yield): ir 1710 (ketone carbonyl) and 3400 cm^{-1} (alcohol); nmr δ1.40 (s, 3H, $-CH_3$), 1.50 (s, 3H, $-CH_3$), 1.18 (dd, 1H, J = 2 Hz, J' = 2 Hz, -CHCO-), 1.30 (dd, 1H, J = 2 Hz, J' = 2 Hz, -CHCO-), 3.24 (t, 2H, J = 8 Hz, $-CH_2OH$), 2.90 (br. s, 1H, -OH) and 7.20 (m, 4H, aromatic protons); ms M^+ 218.1309 (calcd. for $C_{14}H_{18}O_2$: 218.1307). Anal. Calcd. for $C_{14}H_{18}O_2$: C 77.02, H 8.32; Found: C 77.26, H 8.21.

Addition of **2** to Ethyl 2-Carboethoxy-4-methyl-2-pentenoate (**20**)

A solution of ethyl 2-carboethoxy-4-methyl-2-pentenoate (**20**) (214 mg, 1 mmol), S,S'-diethyl dithiomalonate (230 mg, 1.20 mmol) and DABCO (135 mg, 1.20 mmol) in 1,2-dimethoxyethane (20 mL) was stirred at room temperature under an argon atmosphere for 15 hr. The mixture was poured into 2N aqueous hydrochloric acid solution (50 mL) and extracted with dichloromethane (2 ×

20 mL). The combined organic extract was dried, filtered and concentrated. The crude material was chromatographed on silica gel, eluted with 5% ethyl acetate in petroleum ether to afford the pure adduct **21** (386 mg; 95% yield): ir 1735 (ester carbonyl), 1660 and 1690 cm^{-1} (thiolesters); nmr δ0.85 (d, 3H, J = 7 Hz, $-CHCH_3$), 0.98 (d, 3H, J = 7 Hz, $-CHCH_3$), 1.22 (t, 6H, J = 8 Hz, 2× $-COSCH_2CH_3$), 1.30 (t, 6H, J = 8 Hz, 2× $-OCH_2CH_3$), 2.90 (q, 4H, J = 8 Hz, 2× $-COSCH_2CH_3$), 4.20 (q, 4H, J = 8 Hz, 2× $-OCH_2CH_3$), 3.58 (d, 1H, J = 10 Hz, -COCHCO-) and 3.50 (d, 1H. J = 10 Hz, -COCHCO-); ms m/e 345.1370 (M^+-61; calcd. for $C_{16}H_{25}O_6S$: 345.1373). Anal. Calcd. for $C_{18}H_{30}O_6S_2$: C 53.18, H 7.44, S 15.74; Found: C 53.21, H 7.36, S 15.46.

Reduction of Adduct 21

A solution of the adduct **21** (200 mg, 0.49 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The mixture, after stirring at room temperature for 1 hr, was filtered and the residue thoroughly washed with benzene. The filtrate was concentrated and the crude material chromatographed on silica gel. Elution with a 15% ethyl acetate in petroleum ether solution afforded the δ-lactone **22** as a single isomer (73 mg; 70% yield): ir 1735 (ester carbonyl) and 1750 cm^{-1} lactone carbonyl); nmr δ0.84 (d, 3H, J = 7 Hz, $-CH_3$), 0.98 (d, 3H, J = 7 Hz, $-CH_3$), 1.20

(t, 3H, J = 8 Hz, $-OCH_2CH_3$), 4.20 (q, 2H, J = 8 Hz, $-OCH_2CH_3$), 3.40 (d, 1H, J = 8 Hz, -COCHCO-) and 3.85 (t, 2H, J = 8 Hz, $-CH_2OCO-$); ms M^+ 214.1211 (calcd. for $C_{11}H_{18}O_4$: 214.1205). Anal. Calcd. for $C_{11}H_{18}O_4$: C 61.65, H 8.47; Found: C 61.52, H 8.32.

Addition of 2 to 3-Penten-2-one

A solution of 3-penten-2-one (655 mg, 5.20 mmol) in benzene (10 mL) was added to a solution of S,S'-diethyl dithiomalonate (1.00 g, 5.20 mmol) and DABCO (585 mg, 5.20 mmol) in benzene (10 mL). The resulting solution was stirred at room temperature under an argon atmosphere for 24 hr. A 2N aqueous hydrochloric acid solution (30 mL) was added and the mixture extracted with dichloromethane (2 × 20 mL). The combined dichloromethane extract was dried, filtered and concentrated to give the crude product which was chromatographed on silica gel. Elution with a solution of 10% ethyl acetate in petroleum ether afforded the pure adduct **23** (1.25 g; 87% yield) as a light yellow oil: ir 1710 (ketone carbonyl), 1658 and 1680 cm^{-1} (thiolesters); nmr δ1.00 (d, 3H, J = 8 Hz, $-CHCH_3$), 2.11 (s, 3H, $-COCH_3$), 1.27 (t, 6H, J = 8 Hz, 2× $-COSCH_2CH_3$), 2.90 (q, 4H, J = 8 Hz, 2× $-COSCH_2CH_3$) and 3.80 (d, 1H, J = 8 Hz, -COCHCO-); ms m/e 153.0552 ($M^+ - 123$; calcd. for $C_8H_9O_3$: 153.0552). Anal. Calcd. for $C_{12}H_{20}O_3S_2$: C 52.16, H 7.30, [illegible] 23.16; Found: C 51.96, [illegible]

Reduction of the Adduct 23

A solution of the adduct **23** (220 mg, 0.80 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The mixture was stirred at room temperature for 1 hr and then filtered. The residue was thoroughly washed with benzene and the filtrate concentrated. The resulting crude material was chromatographed on silica gel. Elution with 15% ethyl acetate in hexane afforded the pure hydroxy ketone **24** (82 mg; 79% yield): ir 1710 (ketone carbonyl) and 3420 cm^{-1} (alcohol); nmr δ1.00 (d, 3H, J = 7 Hz, $-CHCH_3$), 2.40 (s, 3H, $-COCH_3$), 2.24 (d, 2H, J = 6 Hz, $-CH_2CO-$) and 3.25 (t, 2H, J = 9 Hz, $-CH_2OH$); ms M$^+$ 130.0995 (calcd. for $C_7H_{14}O_2$: 130.0998). Anal. Calcd. for $C_7H_{14}O_2$: C 64.57, H 10.85; Found: C 64.81, H 10.99.

Addition of 2 to 3-carboethoxy-5,5-dimethyl-2(5H)-furanone (25)

To a solution of S,S'-diethyl dithiomalonate (136 mg, 0.70 mmol) and DABCO (79 mg, 0.70 mmol) in 1,2-dimethoxyethane (10 mL), was added a solution of 3-carboethoxy 5,5-dimethyl-2(5H)-furanone (**25**) (100 mg, 0.54 mmol) in 1,2-dimethoxyethane (5 mL). The reaction mixture was stirred at room temperature under an argon atmosphere for 1 hr. Ice-cold 2N aqueous hydrochloric acid solution (20 mL) was added and the mixture extracted with dichloromethane (2 × 20 mL). The combined organic extract was dried, filtered and concentrated. The crude material was chromatographed on silica gel, eluting with 10% ethyl acetate in petroleum ether to afford the pure adduct **26** (200 mg; 100% yield): ir 1730 (ester carbonyl), 1780 (lactone carbonyl), 1660 and 1680 cm^{-1} (thiolesters); nmr δ1.26 (t, 6H, J = 8 Hz, 2× $-COSCH_2CH_3$), 1.32 (t, 3H, J = 8 Hz, $-OCH_2CH_3$), 1.48 (s, 6H, $C(CH_3)_2$), 2.94 (q, 4H, J = 8 Hz, 2× $-COSCH_2CH_3$), 3.66 (q, 2H, J = 8 Hz, $-OCH_2CH_3$), 3.40 (d, 1H, J = 10 Hz, -COCHCO-) and 3.90 (d, 1H, J = 10 Hz, -COCHCO-); ms M^+ 376.1024 (calcd. for $C_{16}H_{24}O_6S_2$: 376.1015). Anal. Calcd. for $C_{16}H_{24}O_6S_2$: C 51.05, H 6.43, S 17.00; Found: C 51.11, H 6.61, S 16.97.

Reduction of the Adduct **26**

A solution of the adduct **26** (170 mg, 0.40 mmol) in benzene (5 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The mixture was stirred at room temperature under an argon atmosphere for 30 min. Filtration and concentration gave the crude material which was chromatographed on silica gel. Elution with a solution of 15% ethyl acetate in petroleum ether afforded the pure alcohol 27 (69 mg; 75% yield) as a single isomer: ir 1735 (ester carbonyl), 1780 (lactone carbonyl) and 3500 cm^{-1} (alcohol); nmr δ1.30 (t, 3H, J = 8 Hz, $-OCH_2CH_3$), 1.45 (s, 6H, $-C(CH_3)_2$), 3.65 (q, 2H, J = 8 Hz, $-OCH_2CH_3$), 2.85 (d, 1H, J = 6 Hz, -COCHCO-) and 3.16

(m, 2H, $-CH_2OH$); ms m/e 185.1045 (M^+-45; calcd. for $C_9H_{13}O_4$: 185.0814). Anal. Calcd. for $C_{11}H_{18}O_5$: C 57.36, H 7.88; Found: C 57.44, H 8.01.

Addition of 2 to Methyl Vinyl Ketone

A solution of S,S'-diethyl dithiomalonate (260 mg, 1.35 mmol) and DABCO (152 mg, 1.35 mmol) in 1,2-dimethoxyethane (10 mL) was stirred at room temperature under an argon atmosphere for 15 min. The mixture was cooled to -30°C and a solution of methyl vinyl ketone (110 mg, 1.60 mmol) in 1,2-dimethoxyethane (5 mL) was added. The reaction mixture was stirred for 48 hr at -30°C and then poured into 2N aqueous hydrochloric acid solution. After extraction with dichloromethane (2 × 15 mL), the combined organic extract was dried, filtered and concentrated. The crude material was purified by column chromatography on silica gel. Elution with 5% ethyl acetate in hexane afforded the mono-adduct **29** (282 mg; 82% yield): ir 1710 (ketone carbonyl), 1660 and 1685 cm^{-1} (thiolesters); nmr δ1.12 (t, 6H, J = 8 Hz, 2× $-COSCH_2CH_3$), 1.84 (s, 3H, CH_3CO-), 2.60 (q, 4H, J = 8 Hz, 2× $-COSCH_2CH_3$) and 3.40 (t, 1H, J = 10 Hz, -COCHCO-); ms m/e 139.0394 (M^+-123; calcd. for $C_7H_7O_3$: 139.0395). Anal. Calcd. for $C_{11}H_{18}O_3S_2$: C 50.38, H 6.87, S 24.43; Found: C 50.38, H 7.00, S 24.73.

Reduction of the Adduct **29**

A solution of the adduct **29** (300 mg, 1,15 mmol) in benzene (10 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The reaction mixture was stirred at room temperature for 1 hr under an argon atmosphere. The mixture was filtered and the residue washed with benzene (3 × 10 mL). The filtrate was concentrated and the crude material chromatographed on silica gel. Elution with 10% ethyl acetate in petroleum ether afforded the pure ketol **30** (114 mg; 86% yield): ir 1710 (ketone carbonyl) and 33410 cm^{-1} (alcohol); nmr δ1.90 (s, 3H, CH_3CO-), 2.30 (t, 2H, J = 6 Hz, $-CH_2CO-$) and 3.70 (m, 2H, $-CH_2OH$); ms m/e 98.0738 (M^+-18; calcd. for $C_6H_{10}O$: 98.0732). Anal. Calcd. for $C_6H_{12}O_2$: C 62.02, H 10.42; Found: C 62.41, H 10.72.

Addition of **2** to cis-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**31**)

A solution of S,S'-diethyl dithiomalonate (200 mg, 1.00 mmol), DABCO (117 mg, 1.00 mmol) and cis-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**31**) (175 mg, 1.20 mmol) in 1,2-dimethoxyethane (15 mL) was stirred at room temperature under an argon atmosphere for 10 hr. A 2N aqueous hydrochloric acid solution (20 mL) was added and the mixture extracted with dichloromethane (2 × 15 mL). The combined dichloromethane extract was dried, filtered and evaporated to dryness. The crude product was purified on silica gel column. Elution with 10% ethyl acetate in petroleum ether gave the Michael adduct **32** (330 mg; 100% yield): ir 1730 (ketone carbonyl), 1660 and 1690 cm^{-1} (thiolesters); nmr δ1.24 (t, 3H, J = 8 Hz, $-SCH_2CH_3$), 1.30 (t, 3H, J = 8 Hz, $-SCH_2CH_3$), 2.96 (q, 2H, J = 8 Hz, $-COSCH_2CH_3$), 2.98 (q, 2H, J = 8 Hz, $-COSCH_2CH_3$), 3.82 (d, 1H, J = 10 Hz, -COCHCO-), 6.16 (dd, 1H, J = 2 Hz, J' = 4 Hz, -CH=CH-) and 6.24 (dd, J = 2 Hz, J' = 4 Hz, -CH=CH-); ms M^+ 338.1008 (calcd. for $C_{17}H_{22}O_3S_2$: 338.1011). Anal. Calcd. for $C_{17}H_{22}O_3S_2$: C 60.34, H 6.56, S 18.91; Found: C 60.39, H 6.59, S 18.86.

Reduction of the Adduct 32

A solution of the adduct **32** (338 mg, 1 mmol) in benzene (10 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL) and the mixture stirred at room temperature under an argon atmosphere for 3 hr. The mixture was filtered and the residue thoroughly washed with benzene. The filtrate was concentrated and purified on silica gel column. Elution with 15% ethyl acetate in petroleum ether afforded the pure ketol **33** (180 mg; 93% yield): ir 1720 (ketone carbonyl) and 3400 cm^{-1} (alcohol); nmr δ3.20 (t, 2H, J = 8 Hz, $-CH_2OH$), 2.50 (s, 1H, OH) and 2.34 (m, 3H, $-CH_2OCH-$); ms M^+ 194.1310 (calcd. for $C_{12}H_{18}O_2$: 194.1307). Anal. Calcd. for $C_{12}H_{18}O_2$: C 74.18, H 9.34; Found: C 74.21, H 9.42.

Addition of **2** to 6-Acetoxy-*cis*-bicyclo[3.2.0]hept-3-en-2-one (**34**)

A solution of S,S'-diethyl dithiomalonate (231 mg, 1.20 mmol), DABCO (135 mg, 1.20 mmol) and 6-acetoxy-*cis*-bicyclo[3.2.0]hept-3-en-2-one (**34**) (183 mg, 1.10 mmol) in 1,2-dimethoxyethane (20 mL) was stirred at room temperature under an argon atmosphere for 48 hr. Ice-cold 2N aqueous hydrochloric acid solution (20 mL) was added and the mixture extracted with dichloromethane (2 × 20 mL). The combined organic extract was dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with 10% ethyl acetate in petroleum ether gave the pure 1,4-adduct **35** (300 mg; 77% yield): ir 1730 (carbonyl), 1660 and 690 cm^{-1} (thiolesters); nmr δ1.26 (t, 3H, J = 8 Hz, $-COSCH_2C\mathbf{H}_3$), 1.28 (t, 3H, J = 8 Hz, $-COSCH_2C\mathbf{H}_3$), 2.96 (q, 2H, J = 8 Hz, $-COSC\mathbf{H}_2CH_3$), 2.98 (q, 2H, J = 8 Hz, $-COSC\mathbf{H}_2CH_3$), 2.12 and 2.06 (both s, total 3H (1:1), CH_3OCO-) and 3.76 (d, 1H, J = 10 Hz, $-COCHCO-$); ms M^+ 358.0912 (calcd. for $C_{16}H_{22}O_5S_2$: 358.0909). Anal. Calcd. for $C_{16}H_{22}O_5S_2$: C 53.63, H 6.15, S 17.88; Found: C 53.86, H 6.26, S 18.01.

Reduction of the Adduct **35**

A solution of the adduct **35** (358 mg, 1 mmol) in benzene (10 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The mixture was stirred at room temperature under an argon atmosphere for 1 hr. It was filtered and concentrated. The resulting crude material was purified on a silica gel column. Elution with 15% ethyl acetate in petroleum ether afforded the pure alcohol **36** (201 mg; 95% yield): ir 1725 (carbonyl) and 3400 cm^{-1} (alcohol); nmr δ2.12 and 2.06 (both s, total 3H (1:1), CH_3OCO-), 3.60 (m, 2H, $-CH_2OH$) and 4.15 (br, s, 1H, OH); ms M^+ 212.1056 (calcd. for $C_{11}H_{16}O_4$: 212.1048). Anal. Calcd. for $C_{11}H_{16}O_4$: C 62.23, H 7.60; Found: C 62.03, H 7.81.

Addition of 2 to 2-cyclohexen-1-one

A solution of S,S'-diethyl dithiomalonate (**2**) (2.31 g, 12 mmol), DABCO (1.35 g, 12 mmol) and 2-cyclohexen-1-one (960 mg, 10 mmol) in benzene (25 mL) was stirred at room temperature under an argon atmosphere for 48 hr. The mixture was poured into ice-cold dilute aqueous hydrochloric acid and extracted with dichloromethane (3 × 25 mL). The combined organic extract was dried, filtered and concentrated to give the crude material which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane afforded the pure adduct **8** (2.68 g; 93% yield) as a light yellow oil: ir 1700 (ketone carbonyl), 1600 and 1690 cm^{-1} (thiol esters); nmr δ1.28 (t, 3H, J = 8 Hz, $-SCH_2CH_3$), 1.27 (t, 3H, J = 8 Hz, $-SCH_2CH_3$), 2.92 (q, 2H, J = 8 Hz, $-SCH_2CH_3$), 2.94 (q, 2H, J = 8 Hz, $=SCH_2CH_3$) and 3.70 (d, 1H, J = 10 Hz, -COCHCO-); ms M^+ 288.0870 (calcd. for $C_{13}H_{20}O_3S_2$: 288.0855). Anal. Calcd. for $C_{13}H_{20}O_3S_2$: C 54.15, H 7.00, S 22.20; Found: C 54.18, H 6.97, S 22.23.

Reduction of adduct **8**

A solution of the adduct **8** (288 mg, 1 mmol) in benzene (10 mL) was added to a suspension of Raney nickel (5 mL, settled volume) in benzene (10 mL). The mixture after stirring at room temperature for 1 hr was filtered, concentrated and purified by column chromatography on silica gel. Elution with a 15% ethyl acetate in hexane afforded the pure alcohol **9** (114 mg; 80% yield) as a colorless liquid; ir 1710 (ketone carbonyl) and 3420 cm^{-1} (alcohol); nmr δ3.50 (t, 2H, J = 9 Hz, $-CH_2OH$), 2.20 (b. s, 1H, OH) and 2.25 (m, 4H, $-CH_2COCH_2-$); ms M^+ 142.0998 (calcd. for $C_8H_{14}O_2$: 142.0994). Anal. Calcd. for $C_8H_{14}O_2$: C 67.56, H 9.93; Found: C 67.58, H 9.92.

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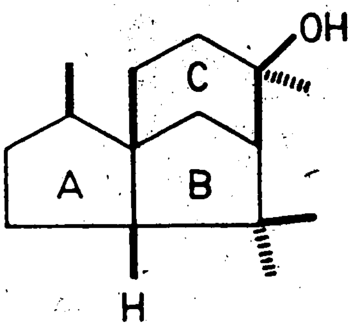
PART 2. CAMPHOR TO CEDROL - A CHEMICAL INVESTIGATION

INTRODUCTION

The tricyclic sesquiterpenes, (+)-cedrol (**1**), (-)-α-cedrene (**2**) and (+)-β-cedrene (**3**), were first isolated by Walter (1) in 1841 from the cedar wood oil of <u>Juniperus virginiana</u>. The structures of these sequiterpenes were the object of a large number of chemical investigations which led to the proposal of no less than thirteen different structures for the tertiary alcohol and the related anhydro-compounds (2). Previous investigators (3,4) incorrectly deduced the size of the unsaturated ring in cedrenes **2** and **3** to be five-membered. It was not until 1953 that the structures of these natural products were correctly and independently assigned by two research groups (5,6).

Stork and Breslow (5) confirmed the size of the unsaturated ring in cedrenes **2** and **3** to be six-membered by a close examination of the infrared spectrum of the anhydride of norcedrene dicarboxylic acid (**4**), a degradation product of the naturally occurring cedrenes. This compound **4** proved to have an infrared spectrum similar to that of glutaric anhydride with absorption peaks at 5.57 and 5.67 μ. A succinic anhydride derivative from a five-membered ring would have been expected to have absorption maxima at 5.40 and 5.63 μ in the infrared spectrum.



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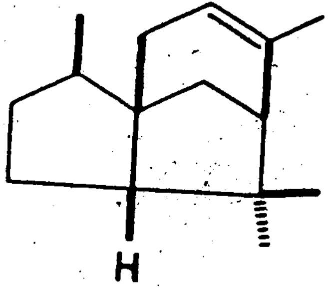

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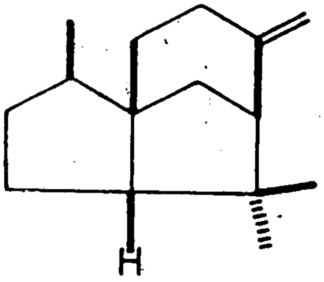

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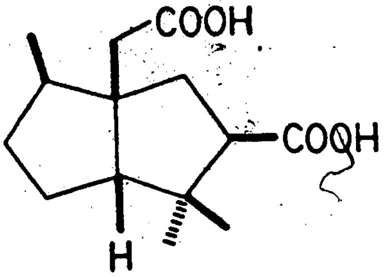

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In 1955, the structures of these tricyclic sesquiterpenes were further confirmed and their relative stereochemistry were correctly determined by a total synthesis (7) of (±)-cedrol (**1**). Buchi and coworkers (8) further established the absolute configuration of the natural products through a chemical correlation of α-cedrene (**2**) with α- and γ-patchoulene.

Cedrenoid compounds have been the subject of considerable synthetic activity. Since the first total synthesis of cedrol (1) was reported in 1955 by Stork, no fewer than a dozen syntheses of the cedrenoid compounds have been accomplished by a number of diverse routes. Interest in the total syntheses of these compounds is widespread largely because of their possession of the relatively rare tricyclo[5.3.1.0]undecane skeleton. The approaches that have been used can be classified into four major types:

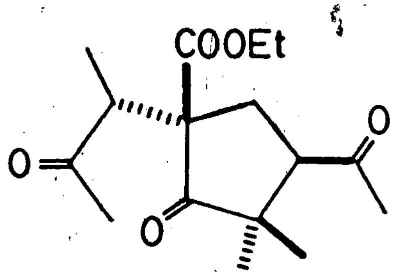
1. Consecutive intramolecular condensation
2. Biogenetic-type synthesis
3. Diels-Alder approach.
4. Arene olefin addition reaction.

Stork and Clarke (7) made use of consecutive intramolecular condensation reactions to construct the tricyclic system. Starting from ring [illegible] they introduced ring A by an aldol process (5→6) and through condensation of the ketoester 7, they obtained the diketone 8 which, after further functional group manipulations, led to (±)-α-cedrene (2).

Eight more syntheses of α-cedrene (2) were reported during the period of 1969 to 1974. All these syntheses mimicked to some extent, a biosynthetic proposal of cedrene (9) which is depicted in Scheme I.

In their first biogenetically patterned synthesis of α-cedrene (2), Corey and coworkers (10) successfully induced cyclization of the diene 9 with boron trifluoride to give the cedrone (10). The diene 9 was obtained in fifteen steps from p-methoxyacetophenone. A similar approach independently used by Crandall and Lawton (11) involved the unsaturated alcohol 11 which underwent ring closure on treatment with formic acid to afford racemic α-cedrene (2). The unsaturated alcohol 11 was prepared from ethyl p-benzyloxyphenylacetate (12).

In 1971, Demole and coworkers (12) applied a cationic cyclization of a spiro[5.6]decane derivative to achieve a synthesis of α-cedrene (2). In their work, β-acoratriene (13), which was readily prepared from nerolidol (14) in four steps, was converted to dehydro-α-cedrene (15) by treatment with boron trifluoride. β-Acoratriene (13) has also been prepared in a more convenient way by Naegli and Kaiser (13).



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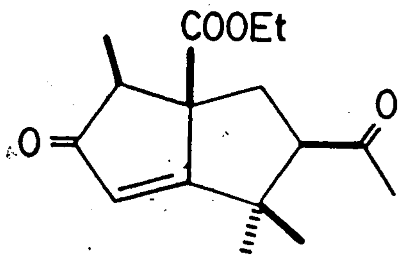

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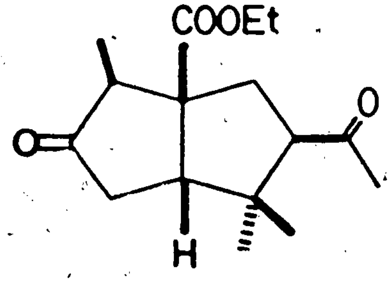

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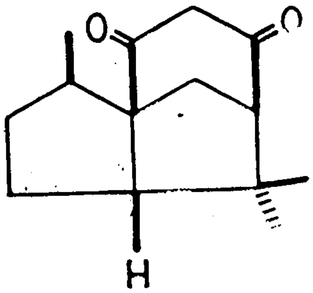

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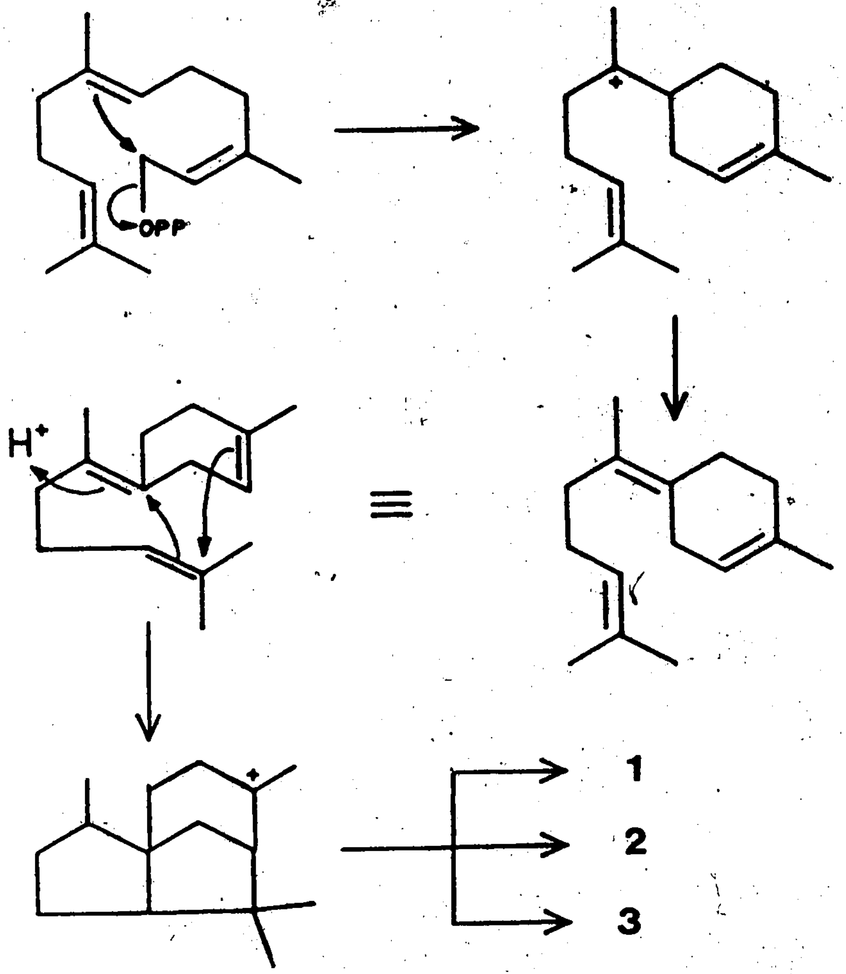
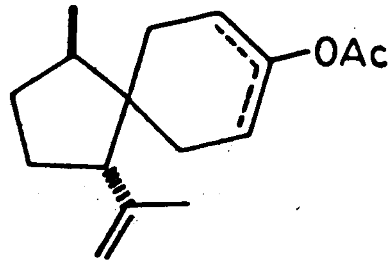
SCHEME I





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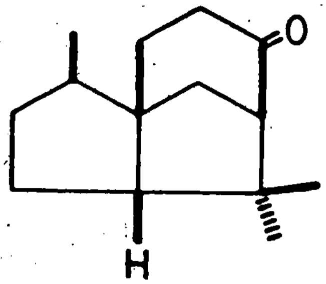

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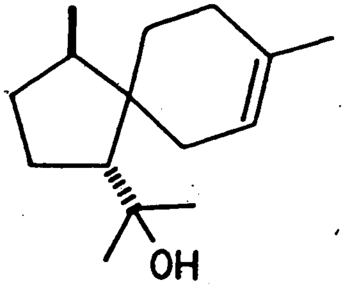

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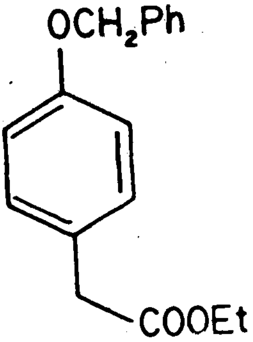

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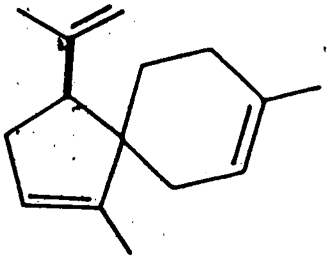

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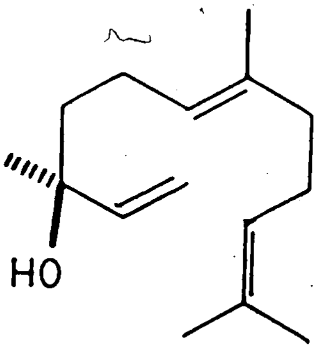

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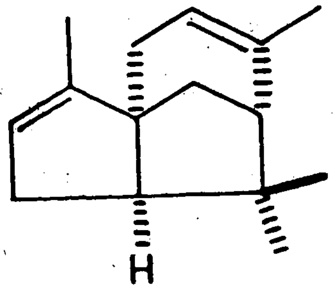
Anderson and Syrdal (14) developed a remarkably simplified transformation of nerolidol (**14**) to α-cedrene (**2**) by treating the former compound sequentially with formic acid and trifluoroacetic acid. Ohta and Hirose (15) obtained α-cedrene (**2**) together with four other cyclization products when they subjected farnesol (**16**) to the treatment of boron trifluoride.

In [illegible] second synthesis of α-cedrene (**2**), Corey's group (16) used a synchronous double annulation process resulting in the direct conversion of the cyclopropyl ketone **17** to cedrone (**10**). This was accomplished by the treatment of **17**, which was prepared from cyclopentane-1,3-dione, with an excess of acetyl methanesulfonate.

Lansbury and coworkers (17) applied a chloro-olefin annulation procedure which they had developed earlier (18) to the synthesis of cedrene. On treatment of the hydroxy chloride **18** with formic acid and acetic anhydride, it underwent cyclization to afford α-cedrene (**2**). Buchi and coworkers (19) in a synthesis of khusimone (**19**) obtained α-cedrene (**2**) as one of the byproducts.

In the last five years, four different routes to the synthesis of the cedrenoids have been accomplished. The first one was by Fallis and Breitholle (20). They made use of an intramolecular Diels-Alder reaction as a key step in the synthesis of (±)-cedrol (**1**) and (±)-cedrene



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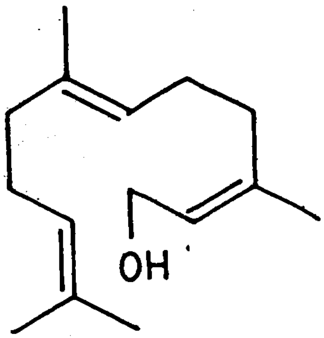

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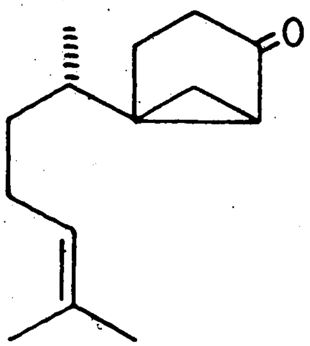

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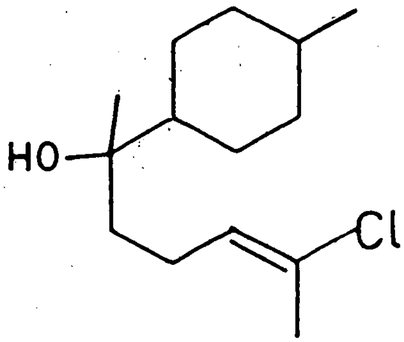

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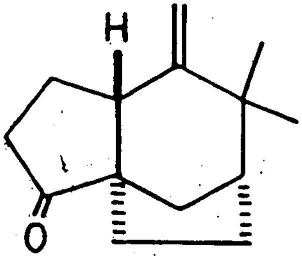
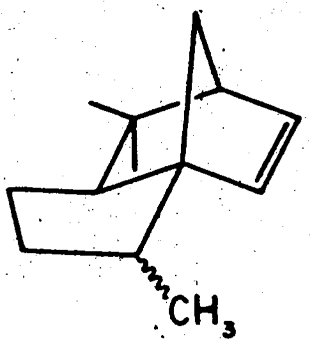


19

(2). Their approach hinged on the generation of a suitable tricyclo[5.2.1.$0^{1.5}$]dec-8-ene intermediate 20 by internal cycloaddition of the cyclopentadiene 21. They correctly anticipated that due to the stereochemical constraints of the system, the fused cyclopentane ring would have the correct exo orientation and that hydroboration of 20 followed by oxidation would generate the desired ketone 22 for ring expansion to cedrone (10). Deslongchamps and coworkers (21) have recently shown that the diketone 23 on treatment with sodium methoxide underwent ring fission to afford enone 24 having the cedrene skeleton. The conversion of 24 to naturally occurring cedrenoids remains to be accomplished.

Wender and Howbert (22) have made use of the 1,3-photoaddition of olefins to arenes as a key step towards the synthesis of cedrene. The intermediate used for the photoaddition was the arene-olefin 25 which was prepared from 2-chloro-5-methylanisole in four steps. Irradiation of the arene-olefin 25 in pentane using Vycor-filtered light from a 450 W Hanovia source gave two cycloadducts 26 and 27. Subsequent treatment of the mixture with bromine resulted in the formation of only 10α- (28) and 10β-bromocedrene-11-one (29), which gave cedrene-11-one 30 on treatment with tri-n-butyltin hydride. Final conversion to α-cedrene (2) was readily accomplished by a Wolff-Kishner reduction.



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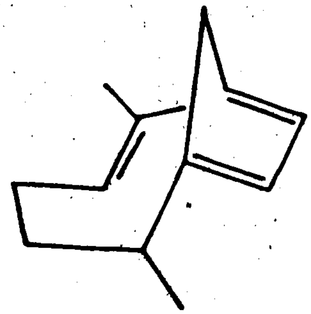

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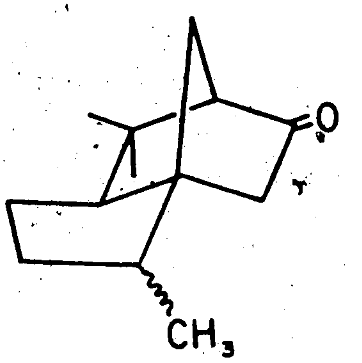

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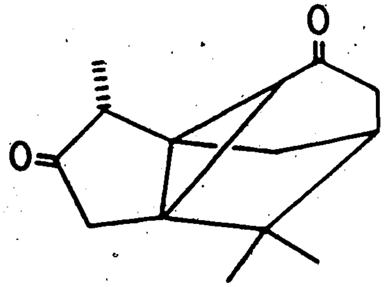

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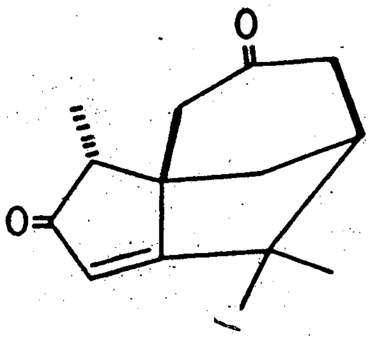

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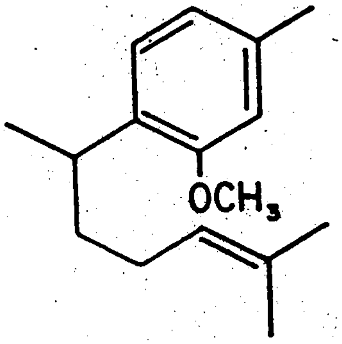

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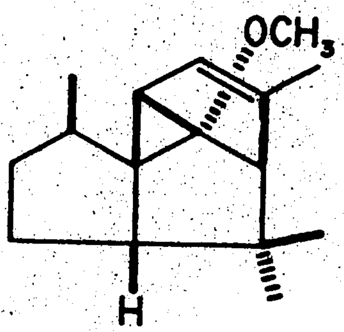

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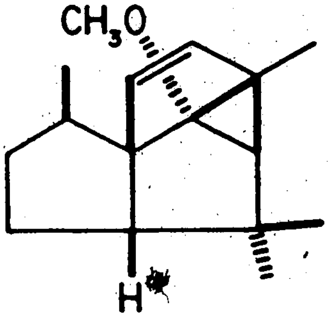

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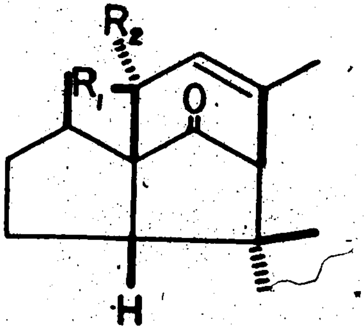
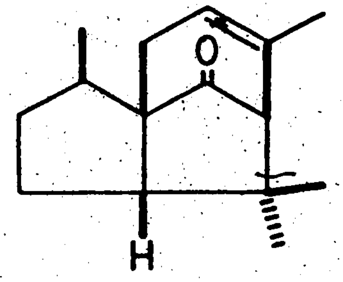


28 $R_1 = H$ $R_2 = Br$

29 $R_1 = Br$ $R_2 = H$



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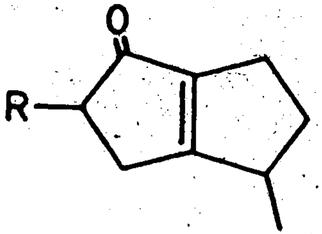
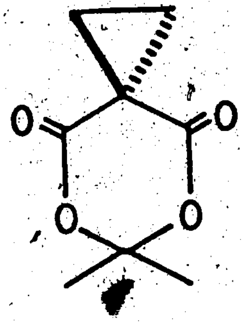
Horton and Pattenden (23) have achieved a total synthesis of (±)-α-cedrene through a sequential intermolecular and intramolecular Michael reaction using bicyclo[3.3.0]octenone **31a** as starting material. In their initial approach they planned to elaborate the tricyclic ring system of cedrene using a single step tandem Michael addition sequence involving the enolate derived from enone ester **31b**. However, although this enolate ion added smoothly to the compound **32** producing the adduct **33**, they were unable to effect the intramolecular Michael reaction required for the formation of the desired compound **34**. The problem was solved when 2-nitro-2-butene was used as a Michael acceptor. The addition of the enolate derived from **31a** to 2-nitro-2-butene gave the nitroketone **35**. Oxidation of **35** afforded the dione **36**, which underwent smooth cyclization to the tricyclo[5.3.1.$0^{1.5}$]-undecanedione **37** on treatment with potassium tert-butoxide. Further functional group manipulations of **37** gave (±)-α-cedrene (**2**).

The sesquiterpene α-acoradiene (**38**) was isolated along with cedrol (**1**) and α-cedrene (**2**) from the wood of Juniperus rigida by Tomita and Hirose (24). When α-acoradiene (**38**) was treated with ethanolic hydrochloric acid, it gave α-cedrene (**2**) in over 80% yield (25). Wolinsky and Solas (26) succeeded in the total synthesis



31 a R = H
b R = CO_2CH_3



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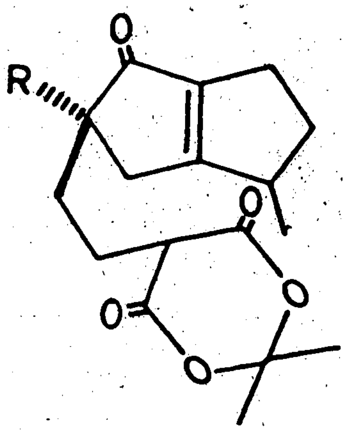
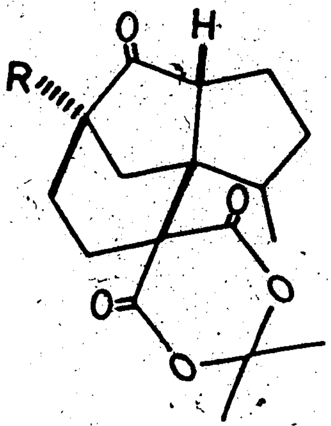
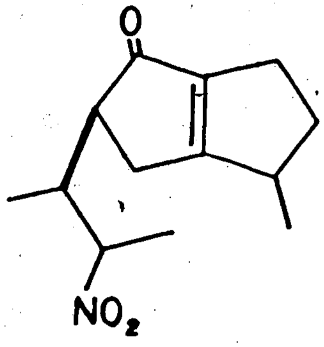


33 R=CO_2CH_3



34 R=CO_2CH_3



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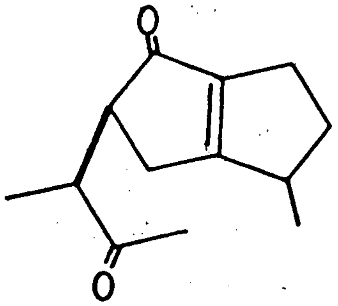

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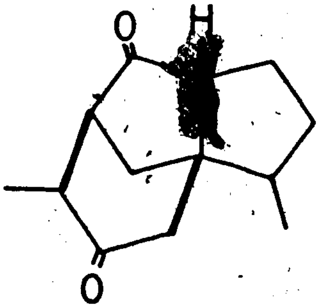

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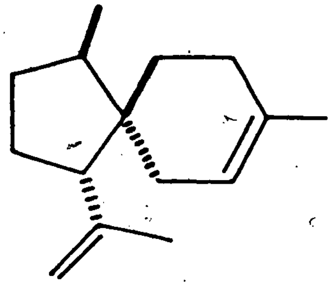
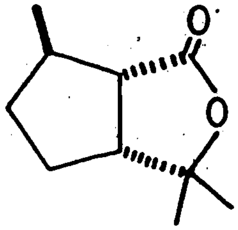


38

of (−)-α-acoradiene (**38**). Their starting material was cis, trans-puleganolide (**39**) which was obtained in three steps (27) from pulegone (**40**). Puleganolide **39** was alkylated with 1-iodo-3,3-ethylenedioxybutane to afford the lactone **41** which underwent elimination with base to give the unsaturated acid **42a**. This acid **42a** was esterified to give the ketal ester **42b**. Hydrolysis of **42b** followed by cyclization with potassium tert-butoxide gave the spirodione **43**. The carbonyl group at C-5 of spirodione **43** was removed by the classic procedure of enolether formation (**43**→**44**) followed by lithium aluminium hydride reduction (28). Acidic workup gave dienone **45**, the conjugated double bond of which was reduced with lithium in ammonia to afford the enone **46** identical with one of the intermediates in Corey's synthesis (10) of cedrol (1). To complete the synthesis of α-acoradiene (38), the dienone **45** was reacted with methylenetriphenylphosphorane followed by a 1,4-reduction of the resulting triene with sodium in liquid ammonia.

About three years ago the synthetic studies presented in Part Two of this thesis were initiated in our laboratories. It was decided at that time to re-examine the synthesis of the cedrenoid compounds when the potential use of camphorsulfonic acid as a starting material was recognized. The availability of



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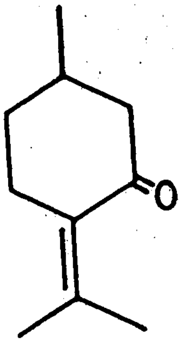

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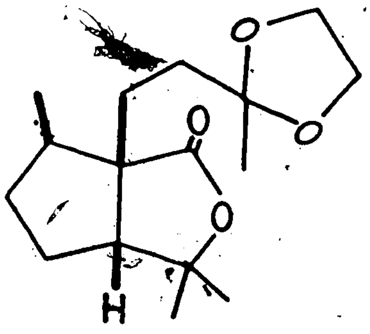

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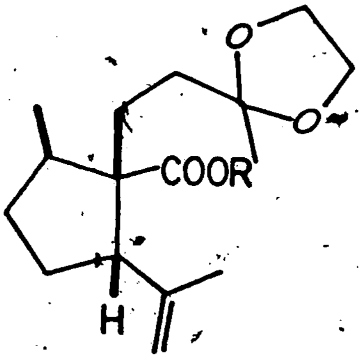
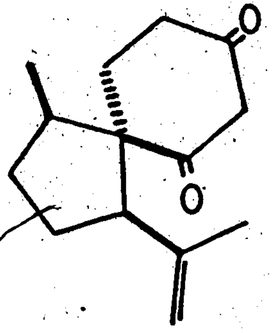


42 a R = H
b R = CH_3



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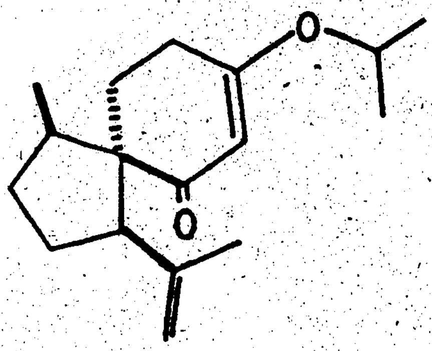

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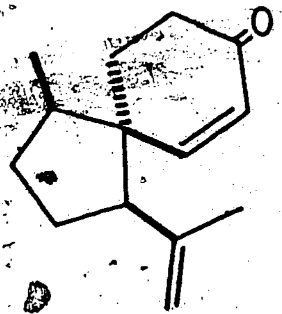

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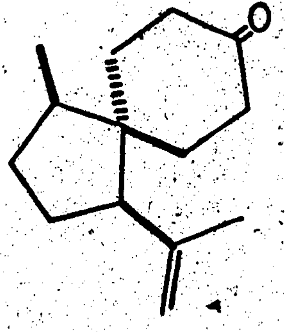

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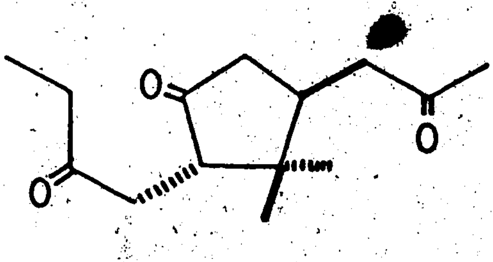

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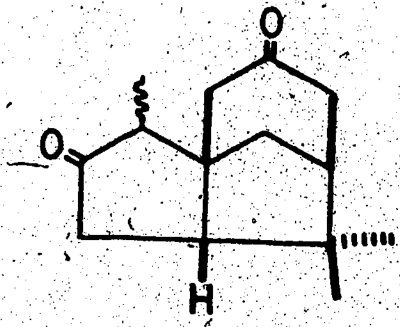

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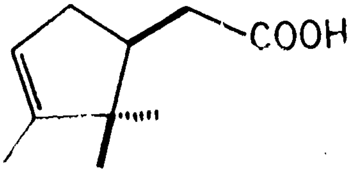
camphorsulfonic acid in both optically active forms provides an excellent opportunity for the synthesis of optically active cedrenoid compounds. In the initial approach, the trione **47** was conceived as a viable key intermediate. It was envisaged that under suitable conditions **47** could undergo consecutive intramolecular aldol condensation and Michael addition to give the triketone **48**. The trione **47** was obtained in optically active form by five operations from (-)-campholenic acid (**49**) which was in turn readily prepared from commercially available l-10 camphorsulfonic acid ammonium salt. The cyclization of **47** to the desired trione **48** was attempted without success. In all cases only the bicyclic enone **50** was obtained.

As a result of the failure to bring about the desired cyclization of **47**, a slightly modified approach was explored. This involved the introduction of a suitably functionalized angular substituent (**50** **51**) with the hope of inducing an internal cyclization of the two side chains to give the required six membered ring. Accordingly several compounds of type **51** were prepared. However all attempts to induce cyclization on these molecules were unsuccessful. The persistent failure to bring about the [illegible] suspicious of the [illegible] derivative **51**. Our



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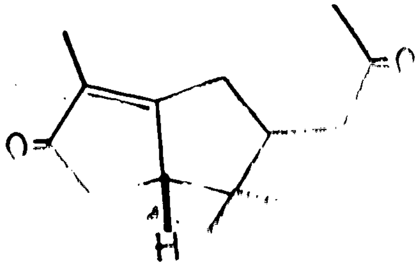

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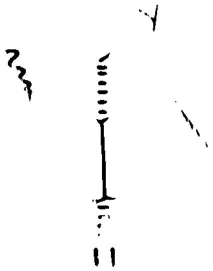
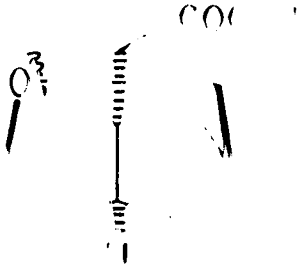
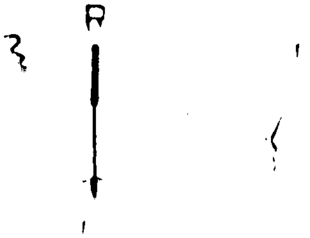
[illegible]



[illegible]





inability to bring about the desired cyclization of **51**, could be due to the wrong relative stereochemistry of the two side chains. The fact that compound **51** ($X=COOCH_3$) was convertible to the tricyclic ether **52** by an array of reactions under conditions which are incapable of bringing about epimerization of any of the pre-existing centres, clearly indicated that the two side chains of this molecule **51** should have been <u>trans</u> to each other. The stereochemistry of **51** should therefore be represented by formula **51a** contrary to expectations.

With these experimental observations in mind the synthetic strategy towards the cedrenoid compounds was modified. It was conceived that a synthesis of cedrol (**1**) by the above strategy would require the reversal of the stereochemistry of the ring B side chain at some point in the synthesis. Such a reversal in stereochemistry could be conveniently brought about if the side chain in question is attached to an epimerizable centre. With this in mind we set out to prepare the bicyclic compound **53** with the indicated absolute configuration. In order to obtain the expected stereochemical requirement in **53** it was apparent that d-10-camphorsulfonic acid would have to be the starting material. Compound **53**, after [illegible] of the carbonyl containing side chain, [illegible] converted to give cedrol (**1**).

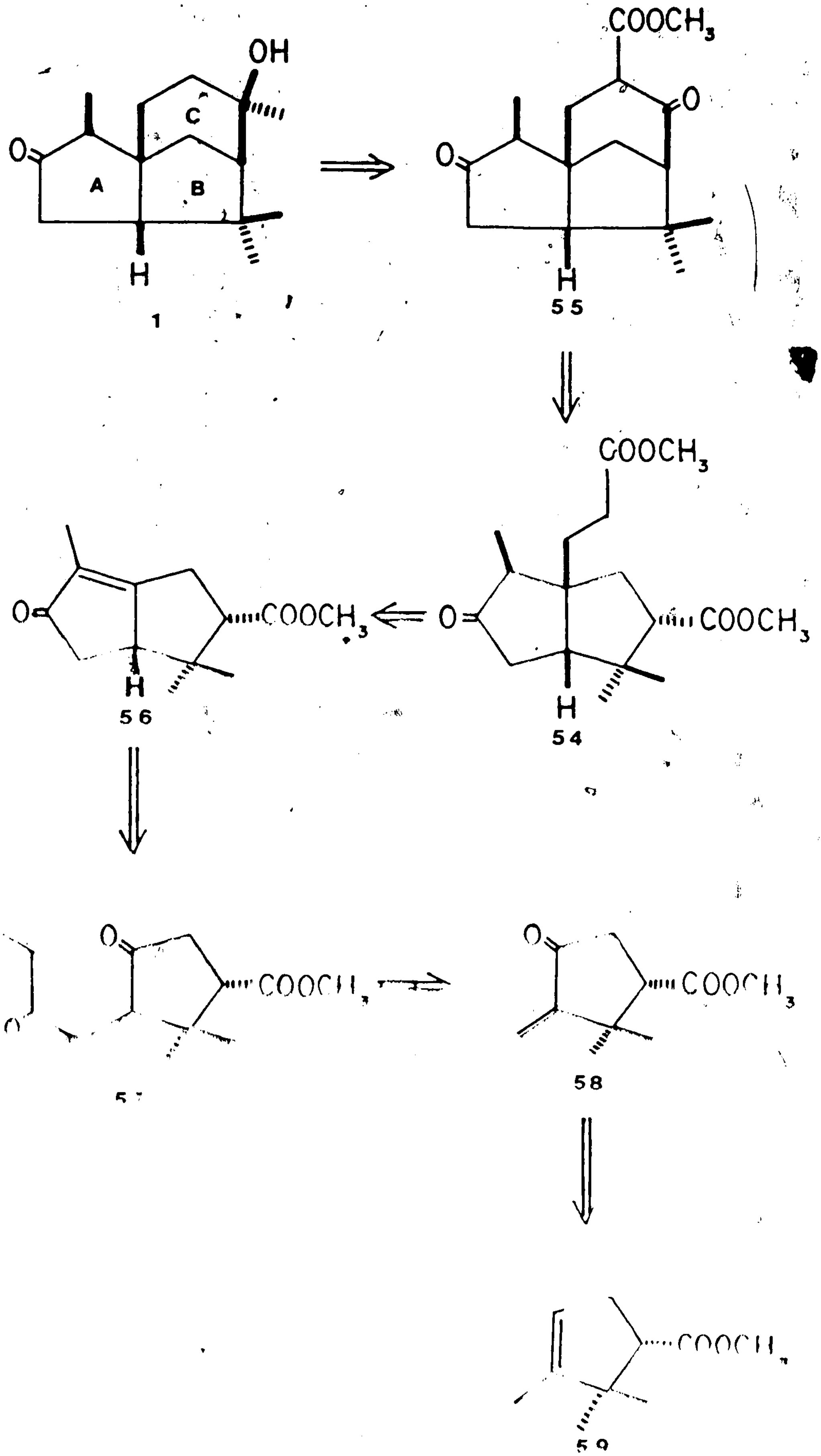
The second part of this thesis describes in detail the work that has been accomplished in this direction towards the synthesis of (+)-cedrol (**1**).

RESULTS AND DISCUSSION

To pursue the synthesis of (+)-cedrol (**1**), our plan was to elaborate the tricyclic ring system present in the cedrenoid skeleton _via_ a bicyclic compound of type **53**. It was conceived that the bicyclic keto diester **54** would be an attractive intermediate. Compound **54** has three highly desirable features: First, it possesses the correct absolute configuration at the ring junction identical with that found in (+)-cedrol (**1**). Secondly, it should be possible under suitable conditions, to epimerize the ester side chain attached to ring B. Thirdly, having brought the two ester side chains to a _cis_ relationship, the ring closure needed to form the tricyclic skeleton could be induced by a Dieckmann reaction. Furthermore, the conditions required for the Dieckmann condensation should, in principle, also effect the needed epimerization, thus facilitating the direct conversion of the bicyclic keto diester **54** to the tricyclic compound **55**.

From a retrosynthetic analysis (Scheme II) it was recognized that a viable synthetic intermediate to the bicyclic keto diester **54** would be the unsaturated ester 59. This compound possesses not only the _gem_-dimethyl

SCHEME II



group and a substitution pattern similar to that found in the bicyclic keto diester **54**, but also functionalities suitable for further modification. For example, after a suitable activation of the vinylic methyl group (**59** → **58**) and the introduction of a three-carbon unit (**58** → **57**), the bicyclic compound **56** could be formed by an intramolecular aldol condensation. Subsequently, a Michael addition of a suitably functionalized unit should then lead to **54**. The potential of camphoric anhydride (**60**) as a good source of the required starting material **59** was also recognized.

Towards the preparation of **59**, d,l-camphoric anhydride (**60**)[1] was treated with methanolic sodium methoxide at room temperature to afford a quantitative yield of the carboxylic acid **61**. The ir spectrum of **61** showed the characteristic broad hydroxyl band at 3300 - 2500 cm^{-1} and a broad carbonyl absorption band centered at 1720 cm^{-1}. The nmr spectrum displayed two three-proton singlets at δ0.85 and 3.70 and a six-proton singlet at δ1.30. The mass spectrum displayed a molecular ion peak at 214.1207 in agreement with the structural formula.

In order to introduce the required olefinic double

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[1] In order to obtain compound **59** with the indicated absolute configuration d-camphoric anhydride would have to be used. The racemic mixture was used in the present work because of its immediate availability.

bond with concomitant removal of the carboxyl group, compound **61** was refluxed with lead tetraacetate and pyridine (28) in benzene. This reaction afforded a 30% yield of an inseparable mixture of the required unsaturated ester **59**[2] and its isomer **62** in a 1:1 ratio. Various attempts were made to improve the yields but no signicant improvement could be attained. Attempts were also made to isomerize **62** to **59**. However, under a variety of acidic conditions both compounds **62** and **59** underwent a 1,2-methyl migration to give the conjugated ester **63**.

In spite of our inability to obtain **59** in a suitable yield and in a pure form, it was decided to carry on the synthesis with the mixture of **59** and **62**, in order to study the feasibility of the subsequent transformations. The mixture was subjected to photooxygenation using methylene blue (29) as a sensitizer. This was followed by reduction of the resulting hydroperoxides with sodium borohydride. The reaction gave a complex mixture from which a small amount (<10%) of the desired allylic alcohol **64** was obtained along with the recovery of a substantial amount of starting material (>50%) even after irradiation for

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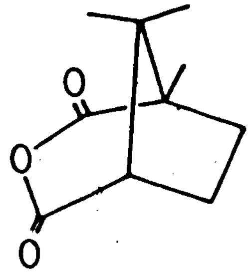
[2] This compound has been obtained previously (30) in 52% yield from ceric ammonium nitrate oxidation of camphorquinone. Unfortunately, we could not reproduce the results.



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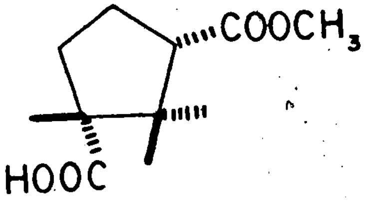

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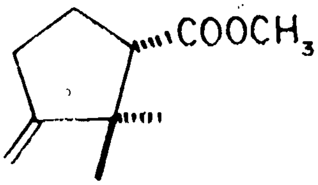

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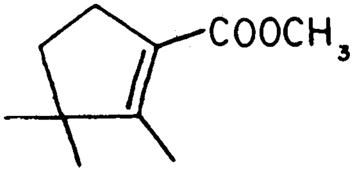

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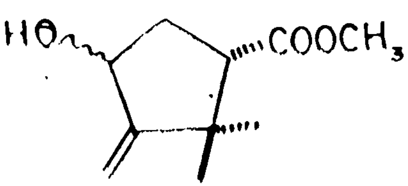

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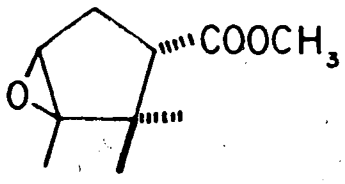


65

more than 7 days. The spectral data confirmed the structure of the allylic alcohol **64**. Its ir spectrum showed diagnostic absorption bands at 3450 (alcohol), 3100, 1665 (olefi[illegible]d 1740 cm^{-1} (ester). The nmr spectrum indicated [illegible]hat the compound was a 1:1 epimeric mixture showing two pairs of methyl singlets, one pair at δ1.20 and 0.95 and the other at δ1.15 and 1.00. In agreement with the structural assignment, two broad singlets at δ5.09 and 4.88 for the two vinylic protons as well as a methyl singlet at δ3.70 were also observed.

Several attempts aimed at improving the yield of the allylic alcohol **64** in the photooxygenation reaction were undertaken. In this direction sensitizers such as rose bengal (31a) and eosin Y (31b) were used in place of methylene blue. In addition the use of solvents such as ethyl acetate and ethanol was also investigated. However, in all cases no substantial improvement of the photochemical reaction was achieved.

The exceptionally low yield of the conversion [illegible] to **64** by the photochemical process prompted an investigation of an alternative route for this conversion. The alternative was a two-step reaction sequence involving epoxidation of the olefinic double [illegible] followed by a ring-opening of the resulting epoxide. Based on literature precedence [illegible] that the base induced ring-opening of epoxide **65** would occur to afford the desired allylic alcohol **64** as a result of the preferential deprotonation of the methyl substituent.

The mixture of unsaturated esters **59** and **62** was treated with m-chloroperbenzoic acid in methylene chloride to afford a 1:1 mixture of epoxides **65** and **66** in quantitative yield. These products were separated by high-pressure liquid chromatography. The nmr spectra confirmed the identity of both epoxides. In addition to a methyl singlet at δ3.70 for the methyl ester, the desired epoxide **65** showed three methyl singlets at δ1.25, 1.20 and 0.95. Furthermore the compound showed a one-proton multiplet at δ3.20, which was assigned to the proton on the epoxide ring. On the other hand, the nmr spectrum of the epoxide **66** showed only three methyl singlets at δ3.70, 1.40 and 1.10 and a two-proton multiplet at δ3.30 which was assigned to the methylene protons on the epoxide ring. The nmr spectra also indicated that each epoxide was a single stereoisomer. The stereochemistry of these epoxides were not determined.

Having obtained the epoxide **65** in the pure form, its ring opening was examined. Thus epoxide **65** was subjected to treatment of lithium diisopropylamide generated *in situ* by the reaction of diisopropylamine and methyl lithium.

Surprisingly, this reaction afforded the desired alcohol **64** only as the minor product (15%) along with a substantial amount of isomeric tertiary alcohol **67**. The allylic alcohol **64** thus obtained was shown to be a single stereoisomer by the nmr spectrum which showed three methyl singlets at δ3.70, 1.15 and 1.00.

Since the allylic alcohol **64** could not be obtained in a reasonable yield from camphoric anhydride, it was necessary to proceed with the synthesis with a slight modification of the intended route (Scheme II). The modification made use of campholenic acid (**68**) as the starting material. This acid was readily available from camphorsulfonic acid by fusion with potassium hydroxide (33). The effective use of campholenic acid (**68**) in the synthesis of (+)-cedrol (**1**) by the intended route (Scheme II) would require a degradation of its acid side chain by one carbon.

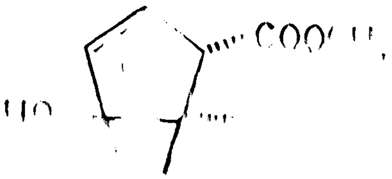
Powdered d-10 camphorsulfonic acid was treated with fused potassium hydroxide to give an 86% yield of (+) campholenic acid **68**. This yield represented an improvement of more than 30% over that obtained by the previous procedure (33). The improvement was achieved by eliminating the process of continuous heating of the fused potassium hydroxide during and after the addition of the camphorsulfonic acid.

Esterification of **68** with [illegible] methyl iodide in acetone (34) at room temperature gave a quantitative yield of the corresponding ester **69**. The structure of the ester **69** was readily established from its spectral data. The ir spectrum showed a carbonyl absorption band at 1745 cm^{-1} and the nmr spectrum displayed methyl singlets at δ3.60 (methyl ester), 1.58 (vinylic methyl), 0.98, and 0.75 (<u>gem</u>-dimethyl). The broad multiplet at δ5.50 was readily assigned to the vinylic proton. A molecular ion peak at 182.1308 in the mass spectrum was consistent with the molecular formula of $C_{11}H_{18}O_2$ which was further confirmed by the elemental analysis.

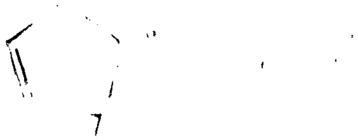
The transformation of methyl campholenate (**69**) to the bicyclic keto diester **54** would require the degradation of the side chain ester by one carbon unit at a suitable stage in the synthesis. Two approaches were successfully examined. One approach involved the degradation of the ester side chain at an early stage while a second approach involved the degradation at a later stage in the synthesis. The details are discussed fully below.

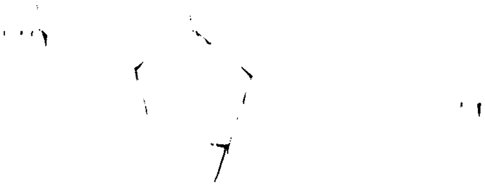
Photooxygenation of **69** using methylene blue as a sensitizer followed by reduction of the resulting hydroperoxides **70** with sodium borohydride gave an epimeric mixture of allylic alcohols **71** in 70% yield. In the ir spectrum, characteristic absorption bands were observed at

66



67





3450 (alcohol), 3100, 1655 (olefin) and 1745 cm^{-1} (ester). The ratio of the two epimeric alcohols was found to be approximately 7:3 as determined by the nmr spectrum which displayed two pairs of methyl singlets, one pair at δ1.15 and 0.85 and the other pair at δ1.05 and 0.95. In agreement with the structural assignment doublets at δ5.15 and 4.94 each with a coupling constant of 8 Hz for the vinylic protons and a singlet at δ3.68 for the methyl ester were also observed. Since the chiral centre bearing the hydroxyl group in **71** was to be destroyed in the subsequent transformations, no attempt was made to separate the two epimeric alcohols.

Although the allylic alcohols **71** could be prepared in good yield by the photochemical process, the reaction suffered from two drawbacks: (1) the reaction required a rather long time (72 hr or more), and (2) for reasons which are not immediately apparent the yield could not be reproduced on a large scale preparation (~5 g). As a result, the following alternative route was successfully examined. Ester **69** was treated with m-chloroperbenzoic acid to give a quantitative yield of two epimeric epoxides **72** which were found to be inseparable. On treatment with lithium diisopropylamide, epoxides **72** afforded the [illegible] allylic alcohols **71** as a 1:1 epimeric mixture (by [illegible] reaction sequence afforded the desired allylic alcohols in a yield comparable to that from the photochemical process. In practice the two-step sequence was preferred over the photochemical process because it required a shorter reaction time and the results were reproducible regardless of the quantities of starting material used.

It is interesting to note that the ring opening of the epoxide 72 gave only the secondary allylic alcohol 71 whereas the ring-opening of the epoxide 65 afforded the tertiary alcohol 67 as the major product. This difference in the experimental results could be rationalized by invoking the higher acidity of the methylene protons of compound 65 compared to the methyl protons due to the close proximity of the ester group.

Initial attempts to oxidize the allylic alcohols 71 with active manganese dioxide (35) gave only 30% yield of the required enone 73. As a result, modified Moffatt oxidation with acetic anhydride and dimethyl sulfoxide (36) was examined. This reaction gave an improved yield of 50%. Further improvement was achieved when the oxidation was performed with oxalyl chloride and dimethyl sulfoxide (37). By this method enone 73 was obtained in 80% yield. The structure of 73 was established by its spectral data. In the mass spectrum, a molecular ion peak [illegible] consistent [illegible]

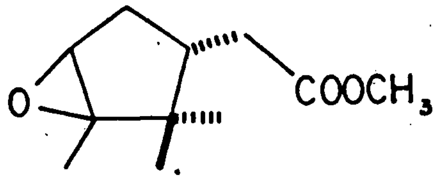
$C_{11}H_{16}O_3$. The nmr spectrum showed three methyl singlets at δ3.68, 1.22 and 1.00. The two broad singlets at δ5.96 and 5.22, each integrating for one proton were assigned to the vinylic protons. The ir spectrum showed diagnostic bands at 1730 (five-membered ketone carbonyl), 1635 (olefin) and 1745 cm^{-1} (ester).

The introduction of a three-carbon unit required for the formation of ring A of cedrol (**1**) was effected by using the method developed by McMurry and coworkers (38). The enone **73** was treated with 1-nitropropane and potassium carbonate at room temperature to give a 72% yield of two isomeric nitroketones **74** in a 2:1 ratio. The ir spectra of the two compounds were found to be similar showing in each case strong carbonyl absorption bands at 1730 and 1745 cm^{-1} and a nitro absorption at 1545 cm^{-1}. In the nmr spectrum the major isomer showed three methyl singlets at δ3.70, 1.08 and 0.64, a methyl triplet (J = 8 Hz) at δ1.00 and a one proton multiplet at δ4.90, whereas the minor isomer showed three methyl singlets at δ3.70, 1.18 and 0.68, a methyl triplet (J = 8 Hz) at δ0.96 and a one proton multiplet at δ4.84. The nmr spectrum further indicated that each of these two compounds was a single stereoisomer. That these two compounds were epimeric at the chiral centre bearing the nitro group was evident from [illegible] experimental results: (1) the two compounds were interconvertible upon base treatment with potassium carbonate, and (2) in the following transformation, both compounds were converted to the same diketone **75**. The stereochemistry of the nitro compounds was tentatively assigned as **74** on the basis of the fact that the compounds were produced under equilibrium conditions and the <u>trans</u> stereochemistry would be expected to be more stable.

The conversion of the nitro compounds **74** to the diketone **75** was accomplished by the treatment of the former compound with one equivalent of sodium methoxide in methanol at room temperature followed by ozonolysis and reductive work up with dimethyl sulfide. The diketoester **75** thus obtained in 82% yield, was a single steroisomer which showed a sharp melting point of 73-75°C and a total of fourteen peaks in the ^{13}C nmr spectrum. The ir spectrum of **75** displayed diagnostic absorption bands at 1715, 1735 (ketone carbonyls) and 1745 cm^{-1} (ester). The nmr spectrum showed four methyl signals, three as sharp singlets at δ3.70, 1.12 and 0.66 and the other as a triplet at δ1.12 with a coupling constant of 8 Hz. Exact mass measurement revealed a molecular weight of 254.1526 in agreement with the required molecular formula of $C_{14}H_{22}O_4$. The absolute stereochemistry of the diketoester **75** was further confirmed by nuclear Overhauser enhancement experiments. When the methyl singlet at [illegible] (one of the geminal methyls) was irradiated, the multiplets at δ2.85 (Ha), 2.70 (Hd) and 2.60 (Hf) showed a 4% enhancement. No enhancement was observed for the multiplet at δ1.85 (Hb). This evidence confirmed the trans relationship between Ha and Hb, and therefore the absolute stereochemistry of the diketo ester **75** must be correct as given.

In order to induce the intramolecular aldol condensation, compound **75** was refluxed with methanolic sodium methoxide. The reaction afforded a mixture of the desired bicyclic ketone **76** along with a variable amount of the corresponding acid **77** which was inevitably formed due to the production of water during the reaction. Without purification the mixture was treated with potassium carbonate and methyl iodide to effect the esterification of the acid component. In this way the bicyclic enone **76** was obtained in a 73% yield. The ir spectrum of **76** displayed absorption bands at 1710 and 1670 cm^{-1} indicating the presence of a conjugated cyclopentenone moiety. The nmr spectrum showed a singlet at δ3.75 for the methyl ester and two singlets at δ1.17 and 0.60 for the gem-dimethyl group. Furthermore, a singlet at δ1.75 was indicative of the vinylic methyl. The appearance of only four singlets in the nmr spectrum further indicated that compound **76** was a single stereoisomer. This was confirmed by the ^{13}C nmr spectrum which displayed only fourteen signals. The absolute stereochemistry of the bicyclic enone **76** was established by nuclear Overhauser enhancement experiments. Irradiation of the methyl singlet at δ1.17 (one of the geminal methyls) resulted in a 6% enhancement of the signals at δ2.55 (Ha) and 2.32 (Hb). On the other hand, irradiation of the methyl singlet at δ0.66 did not effect any enhancement of the signals at δ2.25 (Ha) and 2.32 (Hb). This evidence clearly revealed that the two protons Ha and Hb must be cis to each other supporting the assigned stereochemistry. It is noted that compound **76** has a stereochemistry opposite to that of the precursor **75**, therefore a complete epimerization must have taken place during the aldol condensation.

At this point two primary operations were required to obtain the target bicyclic ketodiester **54**. First, a propionate unit would have to be introduced at the ring junction. Secondly, the existing ester side chain in **76** would have to be reduced by one carbon unit. To fulfill the first requirement, the bicyclic enone **76** was subjected to a Michael reaction with the Grignard reagent prepared from 4-bromo-1-butene in the presence of cuprous iodide. It was envisaged that since the oxidative cleavage of the butenyl group would lead to a propionic acid, the



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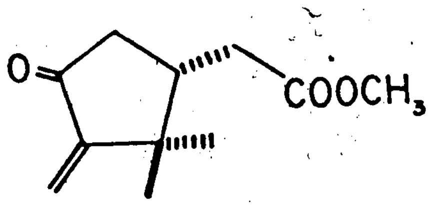

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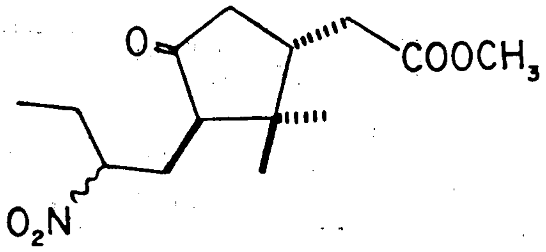
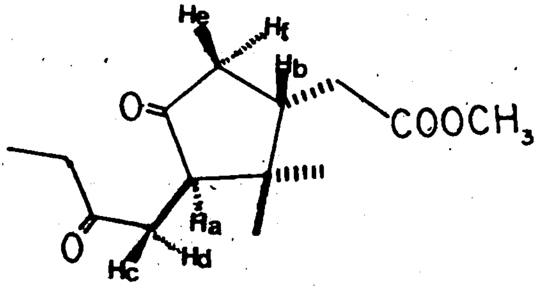
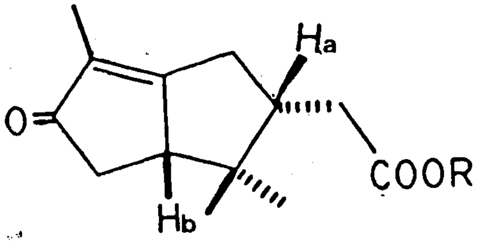


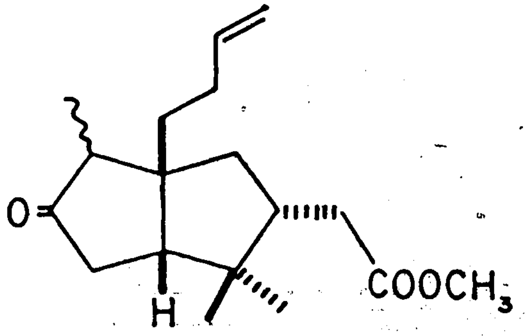
74



75



76 R=CH$_3$
77 R=H



78

introduction of the former could serve as a masked propionate unit. Initially, the 1,4-addition reaction presented some problems. The yield was low and the reaction was erratic. However, after extensive experimental studies, the desired adduct **78** was obtained in a consistent yield of 70% under carefully controlled conditions as follows:

1. The Grignard reagent must be prepared using tetrahydrofuran as solvent; the use of other solvents such as ether and 1,2-dimethoxyethane gave poor results.
2. The commercially available cuprous iodide needed to be freshly purified and extensively dried (39).
3. Six equivalents of the Grignard reagent and 0.3 equivalent of cuprous iodide were needed to achieve an optimum yield of 70%.
4. The mixture of cuprous iodide and the Grignard reagent in tetrahydrofuran needed to be stirred under an argon atmosphere for 90 min at 0°C before the addition of the bicyclic enone **76** at -25°C.
5. After completion of the reaction, the mixture was added slowly to a rapidly stirring solution of 2N aqueous hydrochloric acid.

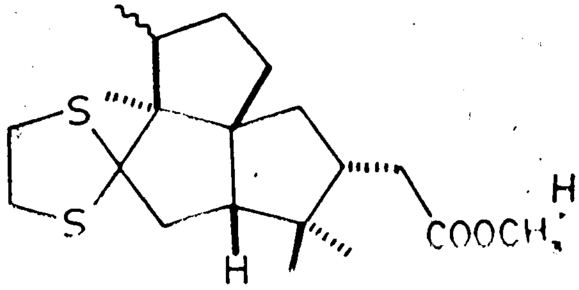
The adduct **78** thus obtained was shown to be a mixture of two inseparable stereoisomers in a 2:1 ratio by the nmr spectrum which showed three methyl singlets at δ0.45, 0.78 and 3.68 and two doublets with the major at δ0.95 and the minor at δ1.02, both with a coupling constant of 6 Hz, for the methyl group adjacent to the ketone carbonyl. In agreement with the structural assignment, the ir spectrum of **78** showed characteristic absorption bands at 1730 (ketone carbonyl), 1745 (ester) and 1650 cm^{-1} (olefin) and the mass spectrum displayed a molecular ion peak at 292.1010. Regarding the stereochemistry, a cis ring junction was assigned based on the known examples (40-44) which showed that the 1,4-addition of organo "ate" complexes to enones occurred preferentially from the sterically less hindered side of the molecule. Moreover, a trans ring function in a bicyclic[3.3.0]octane system would be considerably less favourable.

To degrade the ester side chain of compound **78** it was intended to proceed via a Barbier-Wieland (45) reaction which requires the conversion of the ester into a diphenyl carbinol by a Grignard reaction followed by dehydration and oxidative cleavage of the resulting olefinic double bond. It is anticipated that the latter operation would also effect the oxidative cleavage of the existing olefinic double bond, thus converting simultaneously the angular substituent to the required propionic acid unit.

Since the Grignard reaction with **78** was expected to occur preferentially at the ketone carbonyl, its protection was necessary. Initial attempts made to protect the ketone carbonyl in the form of a ketal using ethylene glycol and p-toluenesulfonic acid failed. The reaction resulted only in the transesterification of the methyl ester with ethylene glycol. Subsequent attempts to convert the ketone to the corresponding thioketal using 1,2-ethanedithiol and boron trifluoride etherate were equally unsuccessful. In this case a tricyclic thioketal **79** was produced in quantitative yield. As a consequence of these results, it was decided to convert the ketone carbonyl of **78** to an alcohol prior to the Grignard reaction. Treatment of compound **78** with sodium borohydride in methanol at 0°C afforded a mixture of hydroxy esters **80** which was separated into two pairs of diastereomers in a 2:1 ratio. In the nmr spectrum the major pair displayed three methyl singlets at δ3.70, 0.85 and 0.65 and doublets at δ0.95 and 1.00, each with a coupling constant of 6 Hz for the methyl close to the hydroxyl group. The minor pair showed three methyl singlets at δ3.70, 0.88 and 0.70 and also two doublets at δ1.02 and 1.00, each with a coupling constant of 6 Hz, for the methyl adjacent to the hydroxyl group. Each pair was independently converted to the same keto diene **84** by the following transformations.

When the major pair of diastereomers of **80** was treated with five equivalents of phenylmagnesium bromide, a quantitative yield of the two diastereomeric diols **81** was obtained. Two closely related routes, were used to convert **81** to the desired keto diene **84**. In one route the secondary hydroxyl group in **81** was first oxidized with pyridinium chlorochromate in dichloromethane. This was followed by refluxing the hydroxy ketone **82** thus formed with a 1:1 mixture of acetic anhydride and acetic acid to afford the keto diene **84** as a 2:1 epimeric mixture in a 60% yield over the two steps. Alternatively, compound **81** was subjected to selective dehydration with p-toluenesulfonic acid at room temperature to give the diene alcohols **83** which were then oxidized with pyridinium chlorochromate in dichloromethane to give the same mixture of **84** in a slightly improved yield of 70%.

The keto diene **84** showed diagnostic absorption bands in the ir spectrum at 1735 (ketone carbonyl) 1600 (aromatic) and 1640 cm^{-1} (olefin). In the nmr spectrum the ten aromatic protons appeared as a multiplet centered at δ7.20 while the vinylic proton close to the phenyl groups appeared as two doublets at δ6.04 and 5.96 in a 2:1 ratio indicating a pair of stereoisomers. The vinylic



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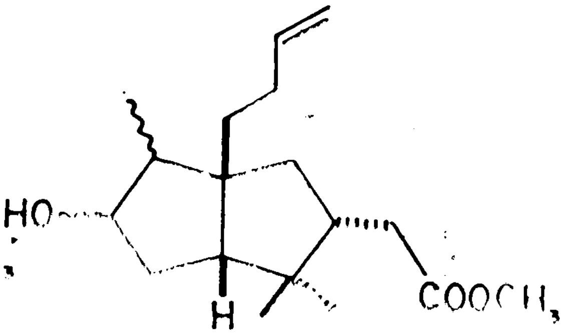
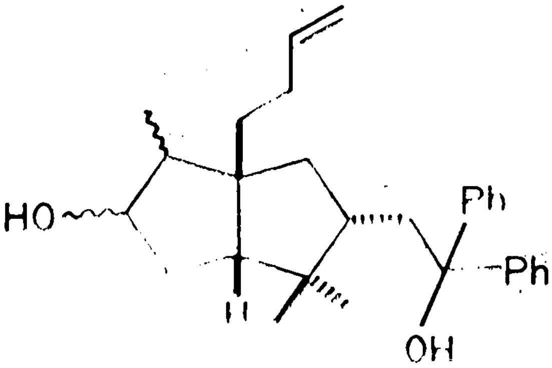
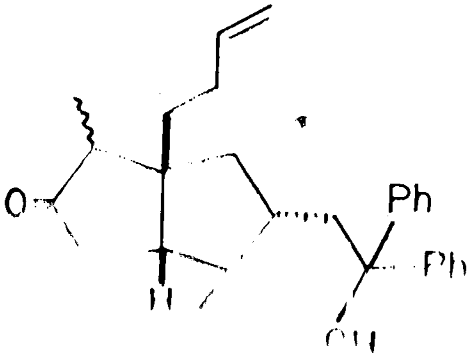


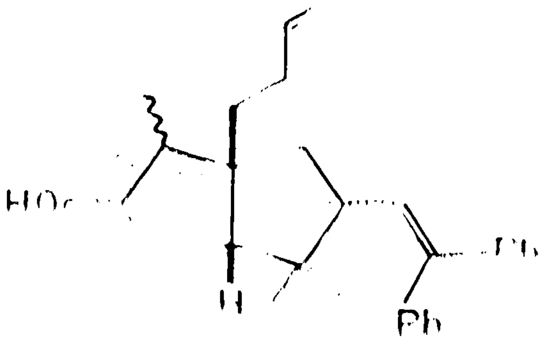
80



81



82



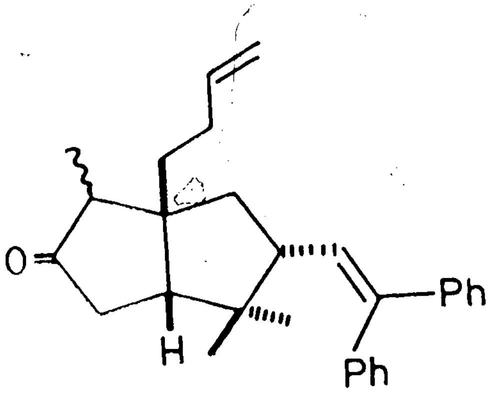
83

protons on the terminal double bond appeared as multiplets at $\delta 5.75$ and 4.95 integrating for one and two protons, respectively. The nmr spectrum also displayed two methyl singlets at $\delta 0.85$ and 0.65 for the gem-dimethyl group as well as two sets of doublets at $\delta 1.02$ and 1.08, in a 2:1 ratio, each with a coupling constant of 6 Hz, for a total of three protons of the methyl group adjacent to the ketone carbonyl.

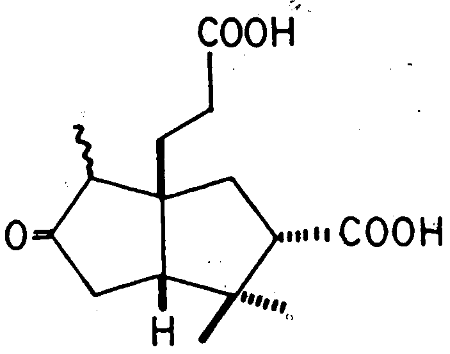
Similar treatment of the minor pair of diastereomers of **80** with phenylmagnesium bromide followed by dehydration with p-toluenesulfonic acid and oxidation with pyridinium chlorochromate gave a 70% yield of the same keto diene **84**.

Since both pairs of **80** were converted to the same keto diene **84** in the same ratio, and since these pairs of compounds showed considerable difference in polarity on thin-layer chromatography, it is not unreasonable to assume that both pairs of stereoisomers differed from each other at the chiral centre bearing the hydroxyl group.

Having obtained the keto diene **84**, we turned our attention to the cleavage of the olefinic double bonds. Keto diene **84** was subjected to ozonolysis followed by reductive work up with dimethyl sulfide. Unfortunately, this reaction gave a complex mixture of inseparable products. Similar results were also obtained when triphenyl phosphine was used as a reducing agent. Attempts were also made to cleave the double bond by ozonolysis with oxidative workup using hydrogen peroxide. The results were equally disappointing. In fact, all attempts to achieve the oxidative cleavage using ozone under a variety of conditions failed to give any detectable amount of the desired compound. Other oxidative cleavage methods were therefore examined. The use of potassium permanganate and sodium periodate (46) also failed to give any promising results. However when **84** was treated with ruthenium tetroxide generated _in situ_ by a catalytic amount of ruthenium dioxide and excess sodium periodate, it smoothly underwent oxidative cleavage to give the diacid **85** which upon esterification with potassium carbonate and methyl iodide afforded the required keto diester **86** in 60% yield and in a 1:1 ratio. The nmr spectrum of **86** displayed two sets of doublets ($J = 6$ Hz) at δ1.00 and 1.20, attributed to the methyl adjacent to the ketone carbonyl. The gem dimethyl group appeared as two singlets at δ1.05 and 0.60. A six proton singlet at δ3.70 was attributed to the two methyl esters. In the ir spectrum, **86** showed diagnostic bands at 1720 (ketone carbonyl) and 1745 cm^{-1} (ester). The mass spectrum displayed a molecular ion peak at 310.3930 consistent with the molecular formula of $C_{17}H_{26}O_5$.



84



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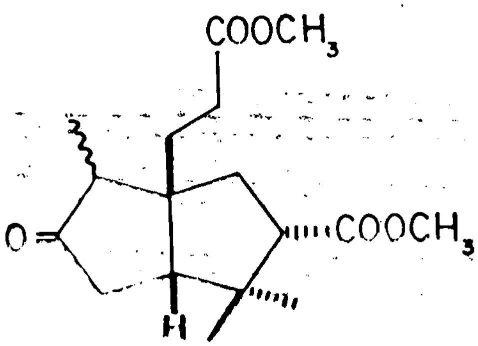
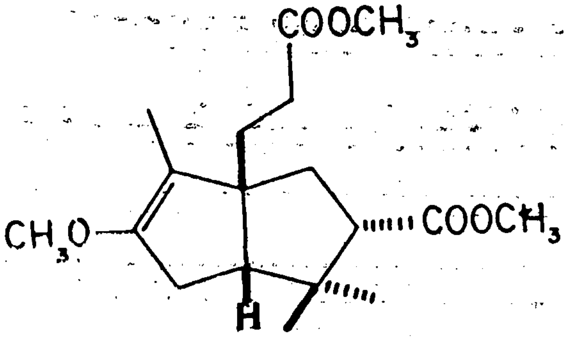


86



87

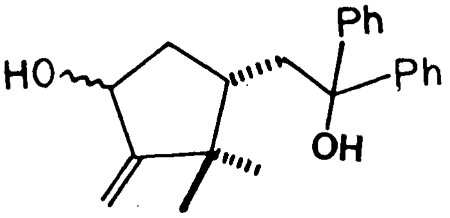
When the keto diester **86** was treated with trimethyl orthoformate and p-toluenesulfonic acid in methanol at room temperature in an attempt to prepare the corresponding dimethyl ketal, the enol ether **87** was formed as a single stereoisomer. This was evident from the nmr spectrum of **87** which displayed only one set of singlets at δ3.65 (2× $-CO_2CH_3$), 3.45 ($-OCH_3$), 1.50 ($=CCH_3$), 1.20 ($-CH_3$) and 0.90 ($-CH_3$). These results clearly indicated that the keto diester **86** must have been epimeric at the chiral centre bearing the methyl group and not at the one bearing the carbomethoxy group.

The second successful approach to the synthesis of bicyclic keto diester **54** from methyl campholenate (**69**) involved an early degradation of the ester side chain. The details of this route are discussed below.

The allylic alcohol **71** was treated with excess phenylmagnesium bromide to afford a diastereomeric mixture of inseparable diols **88** in near quantitative yield. The tertiary hydroxyl group was selectively dehydrated with p-toluenesulfonic acid to afford the hydroxy diene **89** (two epimers) which on oxidation with pyridinium chlorochromate gave the keto diene **90** in 68% yield over the two steps. It was also found that the diols **88** were converted directly to **90** in 80% yield when subjected to oxidation with dimethyl sulfoxide and oxalyl chloride followed by treatment with triethylamine (37). Dienone **90** displayed in the ir spectrum absorption bands at 1630, 1640 (olefin), 1600 (aromatic) and 1720 cm^{-1} (ketone carbonyl). In the nmr spectrum the singlets at δ1.10 and 1.20 were assigned to the gem-dimethyl group and the vinylic protons of the exocyclic double bond appeared as two one-proton singlets at δ5.90 and 5.15. The remaining vinylic proton appeared at δ6.10 as a doublet with a coupling constant of 10 Hz and the aromatic protons appeared as a multiplet at δ7.30. The mass spectrum gave a molecular ion peak at 302.1672 consistent with the molecular formula of $C_{22}H_{22}O$.

In the presence of potassium carbonate dienone **90** reacted with 1-nitropropane in methanol at room temperature to afford two nitro ketones **91** in 71% yield. These two compounds, produced in equal amounts, were separated by column chromatography on silica gel and individually identified. The close similarity of their spectral data indicated that the two compounds were stereoisomers likely due to the centre bearing the nitro group as previously observed for **74**. For further transformation the isomeric mixture was used without separation.

Nitro ketones **91** were converted to **93** by two different routes. Initially, **91** was treated sequentially



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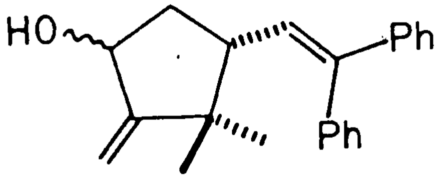

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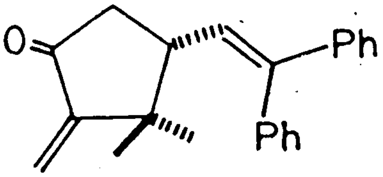

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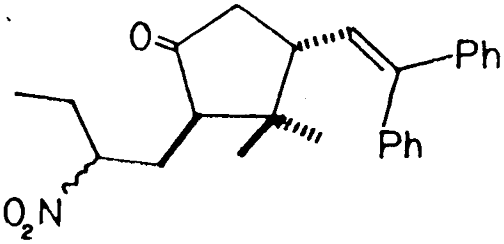

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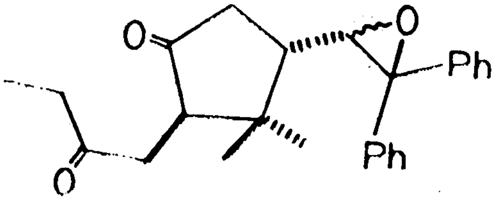

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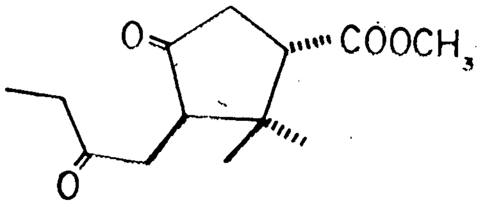


93

with one equivalent of sodium methoxide in methanol and ozone. Reductive work up with dimethyl sulfide afforded two products. The major product which was formed in 56% yield was identified as the diketo epoxide **92** which showed a molecular ion peak in the mass spectrum at 276.2039.

Compound **92** was a mixture of two stereoisomers as evident from the nmr spectrum which displayed two sets of signals for the proton attached to the epoxy ring at δ3.50 and 3.60 each as a doublet (J = 8 Hz). In addition, the gem-dimethyl group appeared also as two sets of singlets; one set at δ0.85 and 0.95 and the other set at δ1.00 and 1.20.

Structure **94** was assigned to the minor product, which was obtained in 15% yield, based on the following spectral data. The ir spectrum showed characteristic absorption bands at 2740 (aldehyde), 1740 (five-membered ketone) and 1720 cm^{-1} (aldehyde and ketone carbonyl). The nmr spectrum showed two sharp methyl singlets at δ0.80 and 1.45 for the gem-dimethyl group and a three-proton triplet at δ1.10 for the methyl of the ketone side chain and a doublet at δ9.80 (J = 4 Hz) for the aldehyde proton. The fact that only one set of signals was displayed in the nmr spectrum strongly suggested that compound **94** was a single stereoisomer.

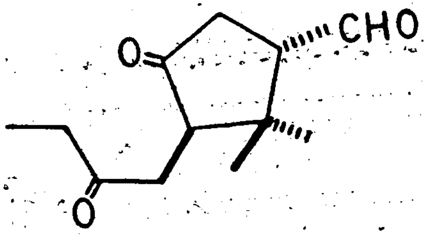
Attempts were made to increase the amount of the desired diketo aldehyde **94** by carrying out the ozonolysis in different solvent systems such as methanol and dichloromethane and at different temperatures ranging from -78°C to 0°C. However, under all the conditions examined the diketo epoxide **92** was always produced in a larger quantity than the desired diketo aldehyde **94**. Fortunately, compound **92** was shown to be readily convertible to the desired compound **94** in 80% yield, when treated with an excess of periodic acid at room temperature. Hence by the treatment of nitroketo olefin **91** with sodium methoxide and ozone followed by cleavage of the epoxide **92** with excess periodic acid it was possible to obtain the desired keto aldehyde **94** in 50% overall yield.

In a slightly modified route compound **94** was prepared from the nitro ketone **91** by the following reaction sequence which eliminated the tedious chromatographic separations involved in the previous preparation. Nitro ketone **91** was subjected to epoxidation with m-chloroperbenzoic acid in dichloromethane and without purification the diastereomeric epoxides **95** were treated sequentially with methanolic sodium methoxide and ozone. Reductive work-up with dimethyl sulfide gave the diketo epoxide **92** which was further degraded with periodic acid to afford the desired keto aldehyde **94** in 70% overall yield.

Compound **94** was oxidized by 0.8N Jones reagent (47) to the corresponding acid which without purification was esterified with potassium carbonate and methyl iodide to afford a 78% yield of the required diketo ester **93** as a single stereoisomer. In the ir spectrum of **93**, carbonyl absorption bands were observed at 1745 (ester), 1730 (five-membered ketone) and 1710 cm^{-1} (aliphatic ketone). In the nmr spectrum geminal methyl groups appeared as two sharp singlets at δ1.30 and 0.70 and the methyl ester as a singlet at δ3.75. In addition the triplet at δ1.15 with a coupling constant of 8 Hz was attributed to the methyl of the butanone side chain. Both the mass spectrum (M^+ 240.3112) and elemental analysis were in complete agreement with the molecular formula of $C_{13}H_{20}O_4$.

The second and more convenient method that was successfuly examined for the cleavage of the olefinic double bond in compound **91** was the use of ruthenium tetroxide. When compound **91** was treated at room temperature with ruthenium tetroxide, generated <u>in situ</u> by the reaction between ruthenium dioxide and sodium periodate, the starting material was consumed within a couple of hours. Initially, work up of the reaction was done by addition of an aqueous potassium carbonate solution and washing with ethyl acetate followed by acidification with dilute aqueous hydrochloric acid. Extraction of the aqueous solution with chloroform afforded the nitro acid **96**. Interestingly, when potassium hydroxide solution was used instead of potassium carbonate in the work up procedure, the diketo acid **97** was obtained. Apparently the latter conditions were sufficient to induce the Nef reaction (48) for the conversion of the nitro group to a ketone. Esterification of the carboxylic acid **97** with potassium carbonate and methyl iodide afforded the required diketo ester **93** as a single stereoisomer in 58% yield from **91**.

Cyclization of compound **93** to the required bicyclic enone **98** was effected by sodium methoxide in refluxing methanol. This reaction afforded a mixture of the required bicyclic enone ester **98** and its corresponding acid **99**. The production of the acid was inevitable due to the generation of water in the reaction medium during the aldol condensation. The acid **99** was readily converted to the ester **98** by treatment with potassium carbonate and methyl iodide. The enone ester **98** thus obtained in a total yield of 80%, was a mixture of two stereoisomers in approximately a 2:1 ratio. The ir spectrum of **98** showed absorption bands at 1700 (ketone carbonyl), 1745 (ester) and 1665 cm^{-1} (olefin). In the nmr spectrum the vinylic methyl appeared as a singlet at $\delta 1.75$ and the <u>gem-</u>



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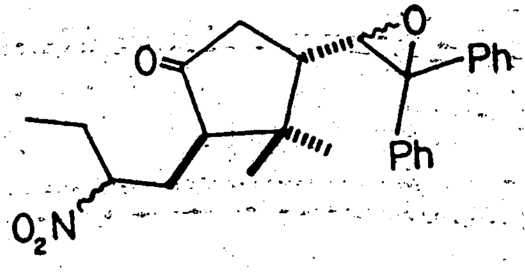

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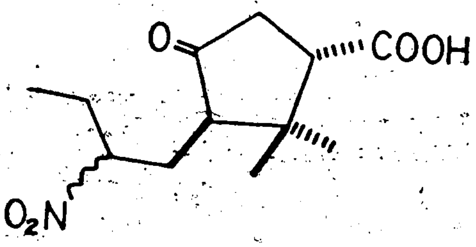

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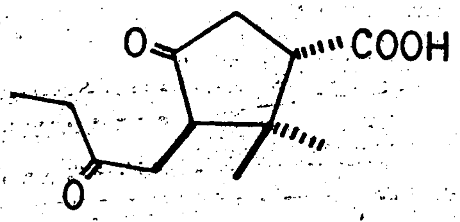

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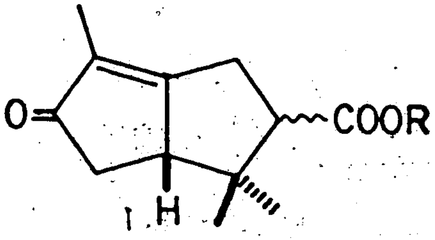


98 R = CH_3

99 R = H

dimethyls as two sets of singlets with the major set at δ1.42 and 0.55 and the minor pair at δ1.12 and 0.80. The methyl of the ester appeared as two close singlets at approximately δ3.75.

To convert the bicyclic enone **98** to the keto diester **54** required the incorporation of a propionate unit into the ring junction of the former compound. This was accomplished by the following transformations.

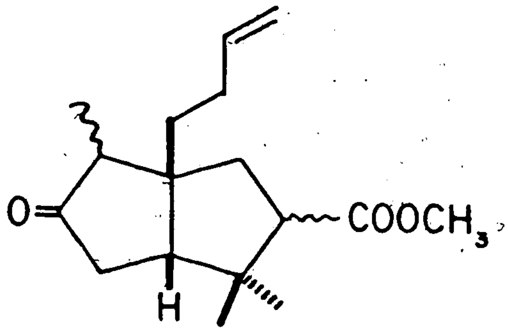
Treatment of enone **98** with 3-butenylmagnesium bromide in the presence of cuprous iodide under carefully controlled conditions described previously for the conversion of **76** to **78** gave a 72% yield of a mixture of diastereomeric keto esters **100** which were inseparable. The ir spectrum of the mixture showed characteristic absorption bands at 1730 (ketone carbonyl), 1745 (ester) and 1640 cm^{-1} (olefin). In the nmr spectrum the methyl adjacent to the ketone appeared as two sets of doublets at δ1.10 and 1.00 both with a coupling constant of 6 Hz. Two close singlets at δ3.70 integrating for a total of three protons was assigned to the methyl of the ester. The _gem_-dimethyl group appeared as two sets of singlets, one set at δ1.20 and 0.65 and the other at δ1.01 and 0.85. The vinylic protons appeared as two multiplets one at δ5.80 integrating for one proton and the other at δ5.00 integrating for two protons. The mass spectrum which displayed a molecular ion peak at 278.4011 confirmed the molecular formula of $C_{17}H_{26}O_3$.

Ozonolysis of compound **100** followed by reductive work up with dimethyl sulfide gave a complex mixture from which the desired aldehyde **101** could not be isolated. However, when triphenylphosphine was used as the reducing agent for the work up, a diastereomeric mixture of aldehydes **101** was formed in good yield. The aldehyde, which was found to be unstable, was oxidized immediately without purification by Jones reagent (47). Esterification of the resulting acid **102** with potassium carbonate and methyl iodide afforded the desired bicyclic keto diester **103** in 38% overall yield.

A considerably simplified method for the cleavage of the terminal double bond of compound **100** made use of ruthenium tetroxide. When compound **100** was treated with ruthenium tetroxide, generated by a catalytic amount of ruthenium dioxide and excess sodium periodate, it afforded the acid **102** which was esterified with potassium carbonate and methyl iodide to give the keto diester **103** in a much improved yield of 65%. The keto diester obtained through the use of ruthenium tetroxide was identical in all respects to that obtained by ozonolysis of **100**.

As expected compound **103** was a mixture of four diastereomers which were inseparable. The nmr spectrum of the diester **103** when compared to that of the epimeric diester **86** obtained by the previously discussed route, was found to be more complex in the methyl region. Furthermore when the diester **103** was treated with trimethyl orthoformate and p-toluenesulfonic acid in methanol at room temperature, in an attempt to make the corresponding dimethyl ketal, two enol ethers **104** were obtained in a 4:1 ratio. The nmr spectrum of this mixture, which was found to be considerably simplified compared to that of the precursor **103**, showed two close singlets at approximately $\delta 3.65$ for a total of six protons for the methyl esters and a singlet at $\delta 1.45$ for the vinylic methyl. The fact that the <u>gem</u>-dimethyl group appeared as two sets of singlets (the major set at $\delta 1.10$ and 0.80 and the minor pair at $\delta 1.00$ and 0.70) clearly indicated the presence of two stereoisomers in **104**.

It is pertinent to point out that the required intermediate diester **54** has now been prepared in two forms by two different routes. In one route the diester was obtained as a mixture of two epimers (i.e. compound **86**) while in the second route the diester was obtained as a mixture of four diastereomers (i.e. **103**). It should be noted that regardless of the number of stereoisomers present in compounds **86** and **103**, both compounds should be synthetically useful for the conversion to cedrol (**1**)



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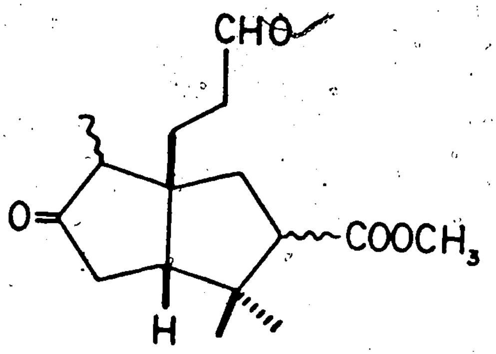

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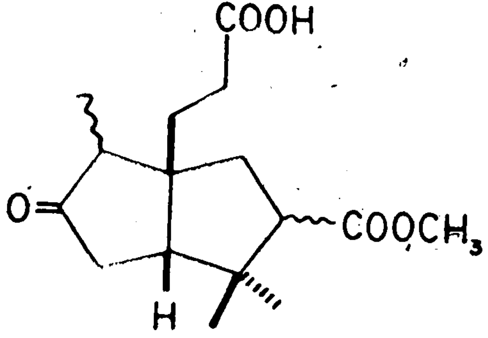

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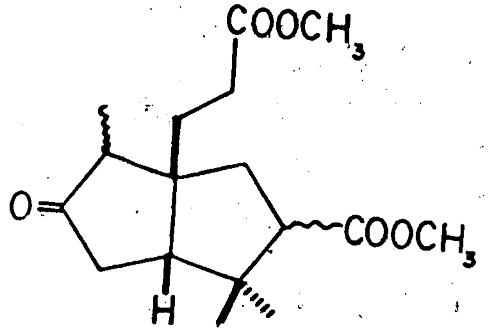

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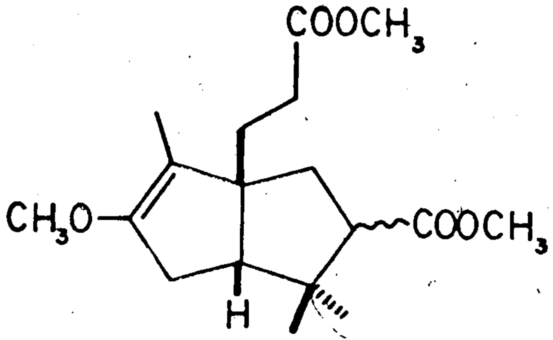


104

is conceivable that the conditions required to induce the intended Dieckmann condensation should also effect the epimerization of the chiral centre bearing the carboxylate group. Of the two epimers regarding the latter centre, only the one having the two ester side chains in the <u>cis</u> relationship would cyclize. With these considerations in mind we attempted the Dieckmann condensation of the diesters 86 and 103 and several of their derivatives.

Initial attempts were made directly on compounds 86 and 103, although it was recognized from the outset that other modes of cyclization, involving either of the two carbons alpha to the ketone and either of the ester groups, were possible. However these reactions leading to the formation of non-enolizable 1,3 diketones should be reversible.

Treatment of compound 103 with sodium hydride in refluxing toluene resulted in a rapid consumption of starting material and the production of a new compound which was shown to be rather non polar by thin layer chromatography on silica gel. However attempts to isolate this compound resulted in its conversion to an acid, esterification of which gave a compound whose nmr spectrum was identical with keto diester 103, with the exception of the relative intensity of the signals. The same results were obtained when diketo ester 86 was treated with [illegible] hydride under similar conditions. Especially the nmr spectrum of the diester produced from **86** was identical to that produced from **103**.

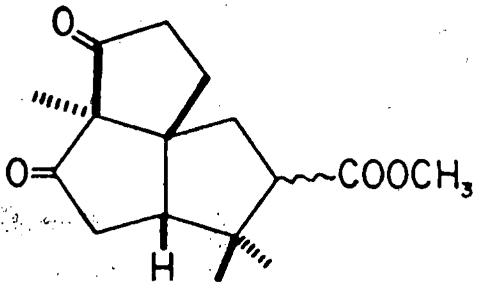
The above findings suggested the following:

1. The attempted Dieckmann condensation of both **86** and **103** might have produced a 1,3-dicarbonyl compound (e.g. **105**) which was easily cleaved to an acid during the work up.
2. The epimerization of the carbon centre bearing the carboxylate group in both compounds must have occurred as expected.

These findings also suggested that in order to effect the Dieckmann condensation the ketone carbonyl needed to be protected in advance. Accordingly, the subsequent studies on the Dieckmann condensation were carried out on enol ethers **87** and **104** as well as the thiol esters **106** and **107**. The latter compounds **106** and **107** were readily prepared from the corresponding keto diesters **86** and **103** by treatment with 1,2-ethanedithiol and boron trifluoride ethereate at 0°C.

The Dieckmann condensation was attempted on each of the enol ethers **87** and **104** and on each of the thiol esters **106** and **107** using the following sets of conditions:

1. Sodium hydride in refluxing toluene in the presence of



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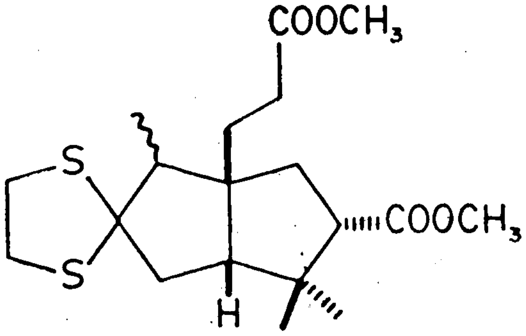

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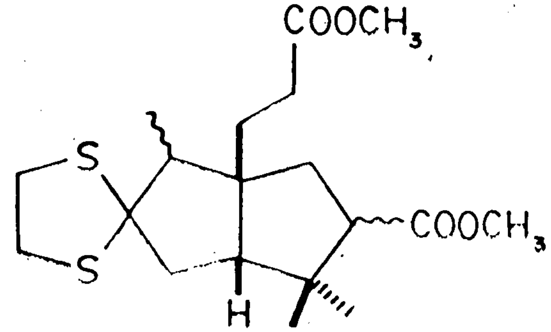

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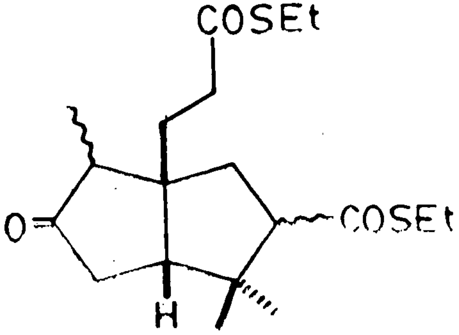

108

a trace of sodium methoxide.

2. Methyl sulfonyl carbanion, produced in situ by NaH and dimethyl sulfoxide at 0°C (49) in dimethylsulfoxide at room temperature and at 60°C.

Unfortunately none of these conditions could induce the desired reaction. The only observations made were the following:

1. Each of the enol ethers **87** and **104** gave a mixture of keto diesters which showed nmr spectra identical with that of **103** with the exception of the relative intensity of the signals. Since the keto diesters were not produced during the reaction as evident from thin-layer chromatography on silica gel, they must have been obtained by the hydrolysis of the enol ethers during the work up for which hydrochloric acid was used.
2. In the case of the thiol esters **106** and **107**, the starting materials were recovered virtually intact. The materials recovered showed nmr spectra identical with that of **107** with the exception of the relative intensities of the signals.

From the above results it can be concluded that the conditions used were insufficient to induce the Dieckmann condensation, although epimerization of the centre bearing the carboxylate unit must have occurred.

In conclusion, the preparation of the target keto diester **54**, a potential intermediate for the total synthesis of cedrol (**1**) has been achieved in two forms (**86** and **103**) from the dextrorotatory camphorsulfonic acid. However, the Dieckmann condensation required for the formation of the tricyclic cedrenoid skeleton needs further investigation in order to arrive at the suitable conditions that would induce the cyclization. It may be possible to bring about the required cyclization to form the six-membered ring in cedrol (**1**) by using the dithiol esters **108**. Dithiol esters have been shown (50) to undergo Dieckmann condensation more easily and under milder conditions than diesters.

EXPERIMENTAL

General

For general remarks see the experimental section of Part 1 of this thesis. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. ^{13}C nmr spectra were recorded on Bruker WP-60 and Bruker HFX-90 spectrometers using deuterated chloroform as solvent and tetramethylsilane as internal standard.

Materials

Tetrahydrofuran was freshly distilled from lithium aluminum hydride. Methanol was purified by refluxing and distilling over magnesium turnings. Dichloromethane was distilled over phosphorus pentoxide. Acetone was treated with potassium permanganate, dried over anhydrous potassium carbonate and distilled. Other solvents were purified by the procedures described in the Experimental Section of Part 1. d-10-Camphorsulfonic acid was obtained from Aldrich Chemical Company.

3-Butenylmagnesium Bromide

A solution of 4-bromo-1-butene (1.88 mL, 0.019 mol) in tetrahydrofuran (10 mL) was added dropwise to magnesium turnings (0.9 g, 0.04 mol) in tetrahydrofuran (10 mL) at 0°C. After the addition the reaction mixture was refluxed under an argon atmosphere for 1 hr. The concentration of the resulting Grignard reagent was determined by adding excess of a known volume of 0.5 M aqueous hydrochloric acid to 1 mL of the Grignard reagent and performing a back titration with 0.5 M aqueous sodium hydroxide solution using phenolphthalein as indicator.

Purification of Cuprous Iodide

Cuprous iodide (13.15 g) was dissolved in a solution of potassium iodide (130 g) in water (100 mL). The resulting solution was shaken for 30 min with decolorizing charcoal (1 g) and the mixture filtered. The filtered solution was diluted with water and pure cuprous iodide precipitated out. The precipitate was collected by suction filtration using a sintered glass-filter (D). The cuprous iodide was washed sequentially with water (4 × 100 mL), absolute ethanol (4 × 100 mL) and ether (6 × 200 mL). The product was powdered and dried under vacuum for four days. During this period the flask containing the cuprous iodide was wrapped with aluminum foil.

(3-Carbomethoxy-1,2,2-trimethylcyclopentyl)carboxylic Acid (61)

d,l-Camphoric anhydride **60** (1.82 g, 10 mmol) was dissolved in methanol (20 mL) and a 0.9 M methanolic sodium methoxide solution (15 mL, 13.5 mmol) was added. The solution was stirred at 0°C under an argon atmosphere for 90 min and then at room temperature for 3 hr. The reaction mixture was poured into ice-cold 2N aqueous hydrochloric acid solution (100 mL) and extracted with dichloromethane (3 × 50 mL). The extracts were dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 15% ethyl acetate in hexane to give the pure product **61** as a light oil (2.0 g; 94% yield): ir 3500 (acid) and 1720 cm^{-1} (carbonyl); nmr δ3.70 (s, 3H, $-CO_2CH_3$), 1.20 (s, 6H, $-C(CH_3)_2$) and 1.60 (s, 3H, $-CH_3$); ms M^+ 214.1207 (calcd. for $C_{11}H_{18}O_4$: 214.1205). Anal. Calcd. for $C_{11}H_{18}O_4$: C 61.65, H 8.47; Found: C 61.68, H 8.52.

4-Carbomethoxy-1,5,5-trimethylcyclopentene (59) and 1-Carbomethoxy-2,2-dimethyl-3-methylidenecyclopentane (62)

Carboxylic acid **61** (12.8 g, 60 mmol) was dissolved in benzene (100 mL). Pyridine (6 mL) and lead tetraacetate

(28.5 g, 64 mmol) were added and the mixture was stirred at room temperature under an argon atmosphere for 1 hr. The mixture was refluxed for 6 hr, cooled to room temperature and poured into ice-cold 2N aqueous hydrochloric acid solution (100 mL). The benzene fraction was separated and washed with cold dilute aqueous sodium carbonate solution and then with water. The organic solution was dried, filtered and concentrated. Column chromatography of the crude material on silica gel, eluting with 5% ethyl acetate in petroleum ether, afforded an inseparable mixture of unsaturated esters **62** and **59** (3.03 g; 30% yield): ir 1745 cm^{-1} (ester). The following nmr data were attributed to **59**: δ0.85, 0.95 (both s, 3H each, $-CH_3$), 1.58 (m, 3H, $CH_3C=$), 3.70 (s, 3H, $-CO_2CH_3$) and 4.80 (m, 1H, $-CH=$). The following nmr data were attributed to **62**: δ1.18, 1.22 (both s, 3H each, $-CH_3$), 3.72 (s, 3H, $-CO_2CH_3$) and 5.20 (m, 2H, $CH_2=$).

4-Carbomethoxy-3,3-dimethyl-2-methylidenecyclopentanol (**64**)

A solution of the mixture of **62** and **59** (2 g, 12 mmol) and methylene blue (100 mg) in methanol (250 mL) was irradiated with two 200 W tungsten light bulbs for 72 hr. During this period a moderate stream of oxygen was bubbled through the solution. The solution was cooled to

0°C and sodium borohydride (0.15 g, 4 mmol) was added. The resulting mixture was stirred for 1 hr, poured into ice-cold 2N aqueous hydrochloric acid solution (200 mL) and extracted with chloroform (3 × 100 mL). The chloroform extract was dried, filtered and concentrated to give the crude residue which was chromatographed on silica gel. Elution with 15% ethyl acetate in petroleum ether afforded the allylic alcohol **64** as a 1:1 mixture of epimeric alcohols (0.11 g; 10% yield): ir 3450 (alcohol) 3100, 1665 (olefin) and 1745 cm^{-1} (ester); nmr δ5.09 (m, 1H, =CH-), 4.88 (m, 1H, =CH-), 3.70 (s, 3H, $-CO_2CH_3$), 1.20, 0.95 (s, 3/2H each, $-CH_3$), 1.15 and 1.00 (s, 3/2H each, $-CH_3$); ms M^+ 184.1102 (calcd. for $C_{10}H_{16}O_3$: 184.1100).

4-Carbomethoxy-1,2-epoxy-2,3,3-trimethylcyclopentane (65) and Apiro[(3-carbomethoxy-2,2-dimethylcyclopentane)-1,1'-oxirane] (66)

A solution of m-chloroperbenzoic acid (80-90% purity, 3.90 g, ~0.019 mol) in dichloromethane (25 mL) was added dropwise to a solution of compounds **59** and **62** (2.30 g, 0.016 mol) in dichloromethane (30 mL) at room temperature. After the addition the reaction mixture was stirred for 2 hr under an argon atmosphere. A 10% aqueous sodium sulfite solution (50 mL) was added to the reaction mixture and the resulting solution was poured into a 10% aqueous sodium bicarbonate solution (50 mL). The organic fraction was separated and washed with water and brine. It was dried, filtered and concentrated. The crude residue was purified by high pressure liquid chromatography to give two epoxides **65** (1.4 g; 47% yield) and **66** (1.35 g; 46% yield).

The following nmr data were obtained for **65**. δ4.80 (m, 1H, -HCO-), 3.70 (s, 3H, CH_3), 1.25 (s, 3H, $-CH_3$), 1.20 and 0.95 (both s, 3H each, $-CH_3$).

The following nmr data were obtained for **66**. δ3.70 (s, 3H, $-CO_2CH_3$), 3.30 (m, 2H, $-CH_2O-$), 1.40 and 1.10 (both s, 3H each, $-CH_3$).

Both compounds **65** and **66** had the following mass spectrum. ms M^+ 184.1100 (calcd. for $C_{10}H_{16}O_3$: 184.1100).

Compound **64** Obtained from 4-Carbomethoxy-1,2-epoxy-2,3,3-trimethylcyclopentane (**65**)

A 1.60 M solution of methyllithium in ether (8.50 mL, 0.014 mol) was added to a solution of diisopropylamine (2.10 mL, 0.015 mol) in ether (20 mL) at -78°C under an argon atmosphere. The mixture was stirred for 30 min and the temperature was raised to -30°C. A solution of **65**

(1 g, 5.4 mmol) in ether (10 mL) was added dropwise. After the addition, the mixture was allowed to warm up gradually to room temperature over a period of 6 hr. The reaction mixure was poured into ice-cooled water (100 mL) and extracted with ether (3 × 50 mL). The extract was dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with 10% ethyl acetate in petroleum ether afforded the tertiary alcohol **67** (0.45 g; 45% yield). Further elution with 15% ethyl acetate in petroleum ether gave the allylic alcohol **64** (0.15 g; 15% yield).

The following spectra data were attributed to the tertiary alcohol **67**: ir 3450 (alcohol) and 1745 cm^{-1} (ester); nmr δ3.70 (s, 3H, $-CO_2CH_3$), 4.85 (m, 2H, -CH=CH-), 1.85 (s, 3H, $-CH_3$), 1.00 and 0.85 (both s, 3H each, $-CH_3$).

The following spectra data were attributed to the allylic alcohol **64**: ir 3500 (alcohol) and 1745 cm^{-1} (ester); nmr δ5.09 (br. s, 1H, =CH-), 4.88 (br. s, 1H, =CH-), 3.70 (s, 3H, $-CO_2CH_3$), 1.15 and 1.00 (both s, 3H each, $-CH_3$).

Both compounds **64** and **67** had an M^+ peak at 184.1102 in the mass spectrum (calcd. for $C_{10}H_{16}O_3$: 184.1100).

(+)-Campholenic acid (**68**)

Potassium hydroxide (250 g, ~3.8 mol) was fused in a porcelain casserole. The heat source was removed and immediately powdered (+)-d-10-camphorsulfonic acid monohydrate (100 g, ~0.40 mol) was added slowly with vigorous stirring over a period of 15 min. The molten mass was allowed to cool to room temperature and then dissolved in water (500 mL). The resulting solution was extracted with chloroform (3 × 300 mL) and the aqueous fraction acidified with ice-cold 2N aqueous hydrochloric acid solution. The acidified solution was extracted with chloroform (3 × 200 mL). The combined organic extract was dried, filtered and concentrated. The crude residue was distilled to give the pure acid **68** (57.8 g; 86% yield): b.p. 97-99°C/0.5 torr; $[\alpha]_D^{25} = +8.6°$ (C = 1.1, $CHCl_3$); ir 3500 (acid) and 1719 cm^{-1} (acid); nmr δ10.90 (br. s, 1H, $-CO_2H$), 5.20 (m, 1H, -HC=), 1.60 (br. s, 3H, $CH_3C=$), 0.90 (s, 3H, $-CH_3$) and 0.79 (s, 3H, $-CH_3$); ms M^+ 168.1144 (calcd. for $C_{10}H_{16}O_2$: 168.1151). Anal. Calcd. for $C_{10}H_{16}O_2$: C 71.38, H 9.59; Found: C 71.41, H 9.72.

4-Carbomethoxymethyl-1,5,5-trimethylcyclopentene (**69**)

A mixture of campholenic acid **68** (30 g, 0.18 mol) and anhydrous potassium carbonate (59.80 g, 0.43 mol) in acetone (250 mL) was stirred at room temperature under an argon atmosphere for 1 hr. Methyl iodide (17 mL, 0.27 mol) was introduced and the mixture stirred for an additional 18 hr. After most of the solvent had been evaporated, the mixture was taken up in chloroform (200 mL) and washed with ice-cold 2N aqueous hydrochloric acid solution (2 × 300 mL), water (2 × 200 mL) and then brine. The organic fraction was dried, filtered and concentrated. The residue was distilled to afford the pure ester **69** (32 g; 97% yield): b.p. 80-82°C/0.6 torr; $[\alpha]_D^{25} = +9.4°$ (C = 1.5, $CHCl_3$); ir 1745 cm^{-1} (ester); nmr δ5.20 (m, 1H, -CH=), 3.60 (s, 3H, $-CO_2CH_3$), 1.58 (br. s, 3H. $CH_3C=$), 0.98 (s, 3H, $-CH_3$) and 0.75 (s, 3H, $-CH_3$); ms M^+ 182.1308 (calcd. for $C_{11}H_{18}O_2$: 182.1307). Anal. Calcd. for $C_{11}H_{18}O_2$: C 72.49, H 9.95; Found: C 72.27, H 9.82.

4-Carbomethoxymethyl-[illegible]-dimethylcyclopentanol (**71**)

A solution of the ester **69** (5.0 g, 28 mmol) and methylene blue (200 mg) in methanol (250 mL) was irradiated with two 200 W tungsten light bulbs for 72 hr. During this period a moderate stream of oxygen was bubbled through the solution. The solution was cooled to 0°C and sodium borohydride (0.30 g, 7.9 mmol) was added. After stirring for 1 hr, it was poured into ice-cold 2N aqueous hydrochloric acid solution (300 mL) and extracted with chloroform (3 × 100 mL). The combined chloroform extract was dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 15% ethyl acetate in petroleum ether to give the pure allylic alcohol **71**[4] (3.90 g; 70% yield): ir 3540 (alcohol), 3100, 1655 (olefin) and 1745 cm^{-1} (ester); nmr δ5.15 (d, J = 8 Hz, -CH-), 4.94 (d, J = 8 Hz, =CH-), 4.40 (m, 1H, -CHOH), 3.68 (s, 3H, $-CO_2CH_3$), 1.15 and 0.85 (both s, 6.3/3 H each, $-CH_3$), 1.05 and 0.95 (both s, 2.7/3 H each, $-CH_3$); ms M^+ 198.1235 (calcd. for $C_{11}H_{18}O_3$: 198.1256). Anal. Calcd. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; Found: C 66.67, H 9.28.

4-Carbomethoxy-1,2-epoxy-2,3,3-trimethylcyclopentane (72)

A solution of m-chloroperbenzoic acid (80-90% purity, 120 g, ~0.07 mol) in dichloromethane (25 mL) was added dropwise to a solution of ester **69** (7.30 g, 0.04 mol) in dichloromethane (50 mL) at room temperature. After the addition, the reaction mixture was stirred for 2 hr under an argon atmosphere and then poured into a 10% aqueous sodium sulfite solution (50 mL). A 10% aqueous sodium bicarbonate solution (50 mL) was added and the organic fraction separated and washed with brine. The organic solution was dried, filtered and concentrated. The crude material was purified on a silica gel column. Elution with 10% ethyl acetate in hexane afforded the pure epoxy ester 72 (7.90 g; 100% yield): ir 1745 (ester) and 1250 cm^{-1} (epoxide); nmr δ3.70 (s, 3H, $-CO_2CH_3$), 1.25 (s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$) and 0.95 (s, 3H, $-CH_3$); ms M^+ 198.1241 (calcd. for $C_{11}H_{18}O_3$: 198.1256). <u>Anal.</u> Calcd. for $C_{11}H_{18}O_3$: C 66.62, H 9.16; Found C 66.69, H 9.31.

<u>71 From Epoxy Ester 72</u>

A 1.60 M solution of methyllithium in ether (18.75 mL, 30 mmol) was added to a solution of diisopropylamine (7 mL, 50 mmol) in ether (20 mL) at -78°C under an argon atmosphere. The mixture was stirred for 30 min and the temperature was raised to -30°C. A solution of the epoxy ester 72 (2.0 g, 10 mmol) in ether (15 mL) was added dropwise. After the addition, the reaction mixture was allowed to warm up to room temperature over a period of 6 hr and then it was poured into ice-cold water (100 mL). The ether fraction was dried, filtered and concentrated. The crude material was purified on a silica gel column, eluting with 15% ethyl acetate in hexane to give the pure allylic alcohol 71 (1.40 g; 70% yield): ir 3450 (alcohol), 3100, 1655 (olefin) and 1745 cm^{-1} (ester); nmr δ5.15 (d, J = 8 Hz, =CH-), 4.94 (d, J = 8 Hz, =CH-), 4.40 (m, 1H, -CHOH), 3.68 (s, 3H, $-CO_2CH_3$), 1.15 and 0.85 (both s, 4.5/3 H each, $-CH_3$), 1.05 and 0.95 (both s, 4.5/3 H each, $-CH_3$); ms M^+ 198.1235 (calcd. for $C_{11}H_{18}O_3$: 198.1256). Anal. Calcd. for $C_{11}H_{18}O_3$: C 66.62, H 9.16; Found C 66.80, H 9.25.

4-Carbomethoxymethyl-3,3-dimethyl-2-methylidenecyclopentanone (73)

A solution of dimethyl sulfoxide (2.88 mL, 0.04 mol) in dichloromethane (10 mL) was added dropwise to a solution of oxalyl chloride (1.80 mL, 0.02 mol) at -78°C under an argon atmosphere. The mixture was stirred for 15 min after the addition and a solution of the hydroxy ester **71** (3.60 g, 0.018 mol) in dichloromethane (20 mL) was added dropwise. The mixture was stirred for 3 hr after the addition and the temperature was allowed to warm up gradually to -30°C. Triethylamine (20 mL) in dichloromethane (20 mL) was added dropwise and the reaction mixture was allowed to warm up gradually to room temperature overnight. It was poured into ice-cold water (200 mL) and the organic fraction separated, washed with water, dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with 5% ethyl acetate in petroleum ether afforded the pure enone **73** (2.80 g; 80% yield): $[\alpha]_D^{25} = +7.5°$ (C = 1.8, $CHCl_3$); ir 1730 (ketone carbonyl), 1745 (ester) and 1635 cm^{-1} (olefin); nmr δ5.96 (br. s, 1H,

=CH-), 5.22 (br. s, 1H, =CH-), 3.68 (s, 3H, $-CO_2CH_3$), 1.22 (s, 3H, $-CH_3$) and 1.00 (s, 3H, $-CH_3$); ms M^+ 196.1301 (calcd. for $C_{11}H_{16}O_3$: 196.100). Anal. Calcd. for $C_{11}H_{16}O_3$: C 67.30, H 8.22; Found: C 67.22, H 8.09.

4-Carbomethoxymethyl-3,3-dimethyl-2-(2-nitrobutyl)cyclopentanone (**74**)

A saturated solution of anhydrous potassium carbonate in methanol (80 mL) was added to a solution of 1-nitropropane (9.40 mL, 105 mmol) in methanol (20 mL). The mixture was stirred at room temperature under an argon atmosphere for 30 min and a solution of the enone **73** (13 g, 70 mmol) in methanol (25 mL) was added. After stirring for 1 hr, the mixture was poured into ice-cold 2N aqueous hydrochloric acid solution (200 mL) and extracted with chloroform (5 × 100 mL). The combined chloroform extract was dried, filtered and concentrated. The resulting crude material was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane afforded the minor isomer of **74** (4.20 g; 24% yield). Further elution with the same solvent system gave the major isomer of **74** (8.30 g; 48% yield). Both isomers of **74** had the following characteristic ir spectrum: 1730 (ketone carbonyl), 1745 (ester) and 1540 cm^{-1} (nitro). Mass spectrum for both isomers of **74**; M^+ 285.1870 (calcd. for $C_{14}H_{23}O_5N$: 285.1577).

The following nmr data were obtained for the minor isomer of **74**: δ4.84 (m, 1H, $-CHNO_2$), 3.70 (s, 3H, $-CO_2CH_3$), 1.18 (s, 3H, $-CH_3$), 0.96 (t, 3H, J = 8 Hz, $-CH_2CH_3$) and 0.68 (s, 3H, $-CH_3$).

The following nmr data were obtained for the major isomer of **74**: δ4.90 (m, 1H, $-CHNO_2$), 3.70 (s, 3H, $-CO_2CH_3$), 1.08 (s, 3H, $-CH_3$), 1.00 (t, 3H, J = 8 Hz, $-CH_2CH_3$) and 0.64 (s, 3H, $-CH_3$).

4-Carbomethoxymethyl-3,3-dimethyl-2-(2-oxobutyl)cyclopentanone (**75**)

To a solution of the major isomer of **74** (2.90 g, 10 mmol) in methanol (25 mL) was added a 0.72 M solution of methanolic sodium methoxide (17 mL, 12 mmol). After stirring at room temperature for 30 min, the resulting solution was chilled to -78°C and a stream of ozone was bubbled through the solution. After 2 hr, the reaction mixture was purged with argon to remove the excess ozone. Methyl sulfide (10 mL) was added and the mixture allowed to warm up to room temperature overnight. It was concentrated and the residue was taken up in dichloromethane, washed with brine, dried, filtered and concentrated. Column chromatography of the crude material on silica gel, eluting with a solution of 10% ethyl acetate in petroleum ether afforded the crystalline diketo ester **75** (2.40 g; 80% yield) m.p. 73-75°C (ether/petroleum ether); $[\alpha]_D^{25}$ = +9.3 (C = 1.0, $CHCl_3$); ir 1715 (ketone), 1735 (five-membered ketone) and 1745 cm^{-1} (ester); nmr δ3.70 (s, 3H, $-CO_2CH_3$), 1.12 (t, 3H, J = 8 Hz, $-CH_2CH_3$), 1.12 and 0.66 (Both s, 3H each, $-CH_3$); ^{13}C nmr δ208.1, 201.7, 166.8, 55.4, 49.9, 40.0, 39.4, 39.2, 35.2, 34.8, 33.0, 24.5, 16.0 and 7.5;; ms M^+ 254.1526 (calcd. for $C_{14}H_{22}O_4$: 254.1519). Anal. Calcd. for $C_{14}H_{22}O_4$: C 66.10, H 8.72; Found: C 66.32, H 8.89.

Similar treatment of the minor isomer of **74** (0.58 g, 2 mmol) in methanol (10 mL) with 0.72 M methanolic potassium methoxide (3.40 mL, 2.4 mmol) followed by ozonolysis at -78°C afforded, after identical work up and purification, the same diketo ester **75** (0.45 g; 75% yield).

7-Carbomethoxymethyl-2,6,6-trimethylbicyclo[3.3.0]oct-1-en-3-one (**76**)

A solution of 0.98 M methanolic sodium methoxide (25.5 mL, 24 mmol) was added to a solution of the diketo ester **75** (4.0 g, 16 mmol) in methanol (25 mL). The resulting mixture was refluxed under an argon atmosphere for 24 hr. After cooling to room temperature, it was poured into ice-cold dilute aqueous hydrochloric acid solution and extracted with chloroform (3 × 50 mL). The chloroform extract was dried, filtered and concentrated to afford a reddish yellow material (4 g) which was dissolved in acetone (20 mL). Potassium carbonate (4 g) was added and the mixture was stirred at room temperature for 30 min. Methyl iodide (1.5 mL) was added and the reaction mixture was stirred for an additional 18 hr, after which most of the solvent was evaporated and the residue taken up in chloroform (50 mL) and washed successively with ice-cold dilute aqueous hydrochloric acid solution, water and brine. The organic solution was dried, filtered and concentrated. The resulting crude material was chromatographed on silica gel. Elution with 10% ethyl acetate in petroleum ether afforded the pure bicyclic enone **76** (2.50 g; 73% yield) as a white crystalline solid: m.p. 56-58°C (petroleum ether/ethyl acetate); $[\alpha]_D^{25} = +5.8$ (C = 1.6, $CHCl_3$); ir 1710 (ketone carbonyl), 1745 (ester) and 1670 cm^{-1} (olefin); nmr δ3.75 (s, 3H, $-CO_2CH_3$), 1.75 (br. s, 3H, $=CCH_3$), 1.17 (s, 3H, $-CH_3$) and 0.60 (s, 3H, $-CH_3$); ^{13}C nmr δ210.1, 180.4, 173.4, 132.3, 55.4, 51.7, 46.7, 41.1, 35.9, 34.6, 31.5, 25.7, 14.4 and 8.3; ms M^+ 236.1422 (calcd. for $C_{14}H_{20}O_3$: 236.1413). Anal. Calcd. for $C_{14}H_{20}O_3$: C 71.18, H 8.47; Found: C 71.23, H 8.57.

1-(3-Butenyl)-7-carbomethoxymethyl-2,6,6-trimethylbicyclo[3.3.0]octan-3-one (78)

A mixture of cuprous iodide (106 mg, 0.56 mmol) in tetrahydrofuran (10 mL) was cooled to 0°C under an argon atmosphere. A solution of 1.04 M 3-butenylmagnesium bromide in tetrahydrofuran (1.2 mL, 13 mmol) was added by syringe and the mixture was stirred for 90 min. The temperature was lowered to -25°C and after 15 min at this temperature, a solution of 76 (500 mg, 2.10 mmol) in tetrahydrofuran (10 mL) was added by syringe. After 10 min the reaction was complete. The mixture was added dropwise to an ice-cold solution of aqueous 2N hydrochloric acid (50 mL) with stirring. It was then extracted with dichloromethane (3 × 25 mL). The combined organic extract was dried, filtered and concentrated. The crude material was purified on a silica gel column. Elution with 5% ethyl acetate in petroleum ether afforded a 1:1 mixture of two inseparable epimeric ketones 78 (430 mg; 70% yield): ir 1735 (ketone), 1745 (ester) and 1650 cm^{-1} (olefin); nmr δ5.80 (m, 1H, -CH=), 5.00 (m, 2H, $=CH_2$), 3.70 (s, 3H, $-CO_2CH_3$), 0.95, 1.02 (both d, J = 6 Hz, total 3H, $-CHCH_3$), 0.45 (s, 3H, $-CH_3$) and 0.78 (s, 3H, $-CH_3$); ms M^+ 292.1010 (calcd. for $C_{18}H_{28}O_3$: 292.2039). Anal. Calcd. for $C_{18}H_{28}O_3$: C 73.92, H 9.65; Found: C 74.81, H 9.78.

1-(3-Butenyl)-7-carbomethoxymethyl-2,6,6-trimethylbicyclo[3.3.0]octan-3-ol (**80**)

Sodium borohydride (130 mg, 3.40 mmol) was added to a solution of **78** (500 mg, 1.70 mmol) in methanol (20 mL) at 0°C under an argon atmosphere. After stirring for 2 hr, the mixture was poured into ice-cold dilute aqueous ammonium chloride solution (100 mL) and extracted with chloroform (3 × 20 mL). The combined chloroform extract was dried, filtered, and concentrated. The crude residue was chromatographed on silica gel. Elution with 10% ethyl acetate in petroleum ether afforded the major pair of isomers of **80** (280 mg; 56% yield). Further elution with 15% ethyl acetate in petroleum ether gave the minor pair of isomers of **80** (140 mg; 28% yield). Both pairs of isomers showed the following ir spectral data: 1745 (ester), 1650 (olefin) and 3400 cm^{-1} (alcohol). Both pairs of isomers had the following mass spectral data: M^+ 294.2200 (calcd. for $C_{18}H_{30}O_3$: 294.2196).

The following nmr data were obtained for the major pair of isomers: δ5.85 (m, 1H, -CH=), 5.00 (m, 2H, $=CH_2$), 4.20 (m, 1H, -CHOH), 3.70 (s, 3H, $-CO_2CH_3$), 0.95 and 1.00 (both d, J = 6 Hz, total 3H, $-CHCH_3$), 0.85 (s, 3H, $-CH_3$) and 0.65 (s, 3H, $-CH_3$).

The following nmr data were obtained for the minor pair of isomers of **80**: δ5.85 (m, 1H, -CH=), 5.00 (m, 2H, $=CH_2$), 4.00 (m, 1H, -CHOH), 3.70 (s, 3H, $-CO_2CH_3$), 1.02 and 1.00 (both d, J = 6 Hz, total 3H, $=CHCH_3$), 0.88 (s, 3H, $-CH_3$) and 0.70 (s, 3H, $-CH_3$).

1-(3-Butenyl)-7-(2-hydroxy-2,2-diphenylethyl)-2,6,6-trimethylbicyclo[3.3.0]octan-3-ol (**81**)

A 2 M solution of phenylmagnesium bromide in ether (6.80 mL, 14 mmol) was added to ether (10 mL) and cooled to 0°C. A solution of the major pair of isomers of **80** (880 mg, 3 mmol) in ether (10 mL) was added dropwise with stirring under an argon atmosphere. After stirring at room temperature for 3 hr, the mixture was poured into ice-cold dilute aqueous ammonium chloride solution and extracted with ether (3 × 20 mL). The combined ether extract was dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 15% ethyl acetate in petroleum ether to afford the diol **81** (1.13 g; 90% yield): ir 1650 (olefin), 600 (aromatic) and 3400 cm^{-1} (alcohol); nmr δ7.20 (m, 10H, aromatic), 5.75 (m, 1H, -CH=), 5.00 (m, 2H, $=CH_2$), 3.70 (s, 3H, $-CO_2CH_3$), 0.85 (s, 3H, $-CH_3$), 0.54 (s, 3H, $-CH_3$), 0.95 and 1.00 (both d, J = 6 Hz, total 3H, $-CHCH_3$); ms M^+ 418.2876 (calcd. for $C_{19}H_{38}O_2$: 418.2873).

Similar treatment of the minor pair of isomers of **80** (500 mg, 1.7 mmol) with phenylmagnesium bromide afforded the corresponding diol **81** (0.66 g; 92% yield): ir 1650 (olefin), 1600 (aromatic) and 3400 cm^{-1} (alcohol); nmr δ7.20 (m, 10H, aromatic), 5.75 (m, 1H, -CH=), 5.00 (m, 2H, =CH$_2$), 3.70 (s, 3H, -CO$_2$CH$_3$), 1.02 and 1.00 (both d, J = 6 Hz, total 3H, -CH$_3$), 0.88 (s, 3H, -CH$_3$) and 0.40 (s, 3H, -CH$_3$); ms M$^+$ 418.2878 (calcd. for $C_{19}H_{38}O_2$: 418.2873).

1-(3-Butenyl)-7-(2-hydroxy-2,2-diphenylethyl)-2,6,6-trimethylbicyclo[3.3.0]octan-3-one (82)

To a suspension of pyridinium chlorochromate (550 mg, 2.60 mmol) and sodium acetate (98 mg, 1.20 mmol) in dichloromethane (20 mL), was added a solution of the diol **81** (from the major pair of isomers of **80**) (500 mg, 1.20 mmol). The mixture was stirred at room temperature for 1 hr under an argon atmosphere. Ether (50 mL) was added and the mixture was filtered through a short pad of Florisil. After most of the solvent had been evaporated, the residue was chromatographed on silica gel. Elution with 5% ethyl acetate in hexane afforded the keto alcohol **82** (400 mg; 82% yield): ir 1730 (ketone carbonyl), 1640 (olefin), 1600 (aromatic) and 3400 cm^{-1} (alcohol); nmr δ7.2 (10H, aromatic), 5.75 (m, 1H, -CH=), 5.00 (m, 2H, =CH$_2$), 3.70 (s, 3H, -CO$_2$CH$_3$), 0.95 and 1.02 (both d, J = 6

Hz, total 3H, $=CHCH_3$), 0.85 (s, 3H, $-CH_3$) and 0.54 (s, 3H, $-CH_3$); ms M^+ 416.2719 (calcd. for $C_{29}H_{36}O_2$: 416.2717).

1-(3-Butenyl)-7-(2,2-diphenylethenyl)-2,6,6-trimethylbicyclo[3.3.0]octan-3-one (84)

A solution of the hydroxy ketone **82** (100 mg, 0.24 mmol) in a mixture of acetic anhydride (4 mL) and glacial acetic acid (4 mL) was refluxed under an argon atmosphere for 24 hr. Most of the solvent was evaporated and the residue was taken up in dichloromethane (20 mL) and washed with ice-cold dilute aqueous sodium bicarbonate solution (3 × 20 mL). The organic fraction was dried, filtered and concentrated. The crude residue was chromatographed on silica gel to give a 1:1 inseparable mixture of the epimeric ketodiene **84** (75 mg; 80% yield): ir 1735 (ketone carbonyl), 1600 (aromatic) and 1640 cm^{-1} olefin); nmr δ7.2-7.5 (m, 10H, aromatic), 6.04, 5.96 (both d, J = 8 Hz, total 1H, $-CH=$), 5.75 (m, 1H, $-CH=CH_2$), 4.95 (m, 2H, $=CH_2$), 1.02, 1.08 (both d, J = 6 Hz, total 3H, $-CHCH_3$), 0.85 (s, 3H, $-CH_3$) and 0.065 (s, 3H, CH_3); ms M^+ 398.2623 (calcd. for $C_{29}H_{34}O$: 398.2611).

1-(3-Butenyl)-7-(2,2-diphenylethenyl)-2,6,6-trimethylbicyclo[3.3.0]octan-2-ol (83)

A solution of the diol **81** (from the major pair of isomers of **80** 760 mg, 1.82 mmol) in dichloromethane (10 mL) was cooled to 0°C and p-toluenesulfonic acid (0.07 g, 0.037 mmol) was added with stirring under an argon atmosphere. After stirring for an additional period of 2 hr, aqueous saturated sodium carbonate solution (20 mL) was added and the organic material extracted with dichloromethane (3 × 20 mL). The combined organic extract was dried, filtered and concentrated. The resulting crude material was purified on a silica gel column. Elution with 10% ethyl acetate in hexane afforded the hydroxydiene **83** (620 mg; 85% yield): ir 3400 (alcohol), 1650 (olefin) and 1600 cm^{-1} (aromatic); nmr δ7.2-7.6 (m, 10H, aromatic), 6.04, 5.96 (both d, J = 8 Hz, total 1H, -CH=), 5.75 (m, 1H, $-CH=CH_2$), 4.95 (m, 2H, $=CH_2$), 0.95, 1.00 (both d, J = 6 Hz, 3H total, $=CHCH_3$), 0.85 (s, 3H, $-CH_3$) and 0.65 (s, 3H, $-CH_3$): ms M^+ 400.2788 (calcd. for $C_{29}H_{36}O$: 400.2768).

Similar treatment of the diol **81** (from the minor pair of isomer of **80**; 380 mg, 0.91 mmol) with p-toluenesulfonic acid (0.035 g, 0.18 mmol) afforded the pure hydroxydiene **83** (300 mg; 83% yield) after purification on a silica gel column. ir 3400 (alcohol), 1650 (olefin) and 1600 cm^{-1}

(aromatic); nmr δ7.2-7.5 (m, 10H, aromatic), 6.00, 5.80 (both d, J = 8 Hz, total 1H, -CH=), 5.75 (m, 1H, $-CH=CH_2$), 4.95 (m, 2H, $=CH_2$), 1.04, 1.02 (both d, J = 6 Hz, total 3H, $-CHCH_3$), 0.88 (s, 3H, $-CH_3$) and 0.40 (s, 3H, $-CH_3$); ms M^+ 400.2788 (calcd. for $C_{29}H_{36}O$: 400.2768).

1-(3-Butenyl)-7-(2,2-diphenylethenyl)-2,6,6-trimethylbicyclo[3.3.0]octan-3-one (**84**)

To a suspension of pyridinium chlorochromate (290 mg, 1.35 mmol) and sodium acetate (80 mg, 0.98 mmol) in dichloromethane (10 mL) was added a solution of the hydroxy diene **83** (from the major pair of isomers of **80**; 360 mg, 0.90 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 2 hr under an argon atmosphere. Ether (50 mL) was added and the mixture was filtered through a short pad of Florisil. The filtrate was concentrated and the residue chromatographed on silica gel. Elution with 5% ethyl acetate in hexane afforded the ketodiene **84** (278 mg; 72% yield): ir 1735 (ketone carbonyl); 1640 (olefin) and 1600 cm^{-1} (aromatic); nmr δ7.30 (m, 10H, aromatic), 6.04, 5.96 (both d, J = 8 Hz, total 1H, -CH=), 1.02, 1.08 (both d, J = 6 Hz, total 3H, $-CHCH_3$), 0.65 (s, 3H, $-CH_3$) and 0.85 (s, 3H, $-CH_3$); ms M^+ 398.2626 (calcd. for $C_{29}H_{34}O$: 398.2611).

Similar treatment of **83** (from the minor pair of isomers of **80**; 300 mg, 0.75 mmol) with pyridinium chlorochromate (242 mg, 1.12 mmol) and sodium acetate (67 mg, 0.82 mmol) afforded the same ketodiene **84** (226 mg; 75% yield).

7-Carbomethoxy-1-carbomethoxyethyl-2,6,6-trimethylbicyclo-[3.3.0]octan-3-one (86)

Ruthenium dioxide (80 mg) was suspended in acetone (30 mL) and a solution of sodium metaperiodate (800 mg) in water (15 mL) was added. The mixture was stirred at room temperature until a clear yellow solution was obtained. Solid sodium metaperiodate (1.0 g) was introduced and a solution of the ketodiene **84** (500 mg, 1.3 mmol) in acetone (10 mL) was then added dropwise with stirring. The reaction mixture was stirred for 4 hr and isopropyl alcohol (10 mL) was added. After 30 min the mixture was filtered and the residue thoroughly washed with acetone. Most of the solvent was evaporated and the aqueous solution made basic with 1N aqueous potassium hydroxide solution. The solution was washed with ethyl acetate (3 × 30 mL) and the aqueous fraction was acidified with 1N aqueous hydrochloric acid solution. Extraction with chloroform (3 × 30 mL) was followed by drying of the chloroform extract. Filtration and concentration gave the crude acid (500 mg) which was dissolved in acetone (10 mL). Potassium carbonate (500 mg) was added and the mixture stirred at room temperature for 30 min. Methyl iodide (0.5 mL) was added and the mixture stirred for 24 hr. The resulting mixture was poured into ice-cold dilute aqueous hydrochloric acid and extracted with chloroform (3 × 20 mL). The chloroform extract was dried, filtered and concentrated. The resulting crude material was chromatographed on silica gel. Elution with 10% ethyl acetate in petroleum ether afforded the ketodiester **86** (242 mg; 60% yield): ir 1745 (ester) and 1720 cm^{-1} (ketone carbonyl); nmr δ3.70 (s, 6H, 2× $-CO_2CH_3$), 1.00, 1.20 (both d, J = 6 Hz, total 3H, $-CHCH_3$), 1.06 (s, 3H, $-CH_3$) and 0.60 (s, 3H, $-CH_3$); ms M^+ 310.3930 (calcd. for $C_{17}H_{26}O_5$: 310.3929). Anal. Calcd. for $C_{17}H_{26}O_5$: C 65.79, H 8.44; Found: C 65.88, H 8.71.

7-Carbomethoxy-1-carbomethoxyethyl-3-methoxy-2,6,6-trimethylbicyclo[3.3.0]oct-2-ene (**87**)

A solution of the ketodiester **86** (200 mg, 0.64 mmol), trimethyl orthoformate (0.09 mL, 0.75 mmol) and p-toluene sulfonic acid (5.60 mg, 2.8 × 10^{-3} mmol) in methanol (10 mL) was stirred at room temperature under an argon atmosphere for 24 hr. Ice-cold 10% aqueous sodium bicarbonate solution (20 mL) was added and the mixture extracted with chloroform (3 × 20 mL). The combined extract was dried, filtered and concentrated. The crude residue was chromatographed on silica gel. Elution with 5% ethyl acetate in petroleum ether afforded the pure enol ether **87** (151 mg; 70% yield): ir 1740 cm^{-1} (ester); nmr δ3.65 (s, 6H, 2X-CO_2CH_3), 3.45 (s, 3H, -OCH_3), 1.50 (s, 3H, =CCH_3), 1.20 and 0.90 (both s, 3H each, -CH_3); ms M^+ 324.1936 (calcd. for $C_{18}H_{28}O_5$: 324.1937). Anal. Calcd. for $C_{18}H_{28}O_5$: C 66.62, H 8.70; Found: C 66.79, H 8.91.

4-(2-Hydroxy-2,2-diphenylethyl)-3,3-dimethyl-2-methylidenecyclopentanol (**88**)

A 2 M solution of phenylmagnesium bromide in ether (7.30 mL, 15 mmol) was added to ether (10 mL) and cooled to 0°C. A solution of the hydroxy esters 71 (580 mg, 15 mmol) in ether (10 mL) was added dropwise with stirring. After stirring for an additional 3 hr at room temperature, the mixture was poured into ice-cold 2N aqueous hydrochloric acid solution (50 mL) and extracted with ether (3 × 20 mL). The combined ether extract was dried, filtered and concentrated. The residue was subjected to column chromatography on silica gel. Elution with 10% ethyl acetate in hexane afforded the diol **88** (870 mg; 90% yield): ir 3450 (alcohol), 1655 (olefin) and 1600 cm^{-1} (aromatic); nmr δ7.30 (m, 10H, aromatic), 5.20 (d, J = 8

Hz, 1H, =CH-), 4.95 (d, J = 8 Hz, 1H, =CH-), 4.45 (m, 1H, -CHOH), 1.05 (s, 3H, -CH_3) and 0.85 (s, 3H, -CH_3); ms M^+ 322.1922 (calcd. for $C_{22}H_{26}O_2$: 322.1934). Anal. Calcd. for $C_{22}H_{26}O_2$: C 81.94, H 8.13; Found: C 81.78, H 8.06.

3,3-Dimethyl-4-(2,2-diphenylethenyl)-2-methylidenecyclopentanol (**89**)

p-Toluenesulfonic acid (0.23 g, 1.20 mmol) was added to a solution of the diol **88** (2.00 g, 6.24 mmol) in dichloromethane (25 mL) and the mixture was stirred at 0°C under an argon atmosphere for 3 hr. Saturated aqueous sodium carbonate (150 mL) was added and the mixture was extracted with dichloromethane (3 × 50 mL). The combined extract was dried, filtered and concentrated. The crude material was chromatographed on silica gel eluting with 5% ethyl acetate in hexane to give the hydroxy diene **89** (1.70 g; 90% yield): ir 1630, 1640 (olefin), 3450 (alcohol), and 1600 cm^{-1} (aromatic); nmr δ7.30 (m, 10H, aromatic), 6.00 (d, J = 10 Hz, 1H, -CH=), 5.20 (d, J = 8 Hz, 1H, =CHH), 4.95 (d, J = 8 Hz, 1H, -CHH), 4.45 (m, 1H, -CHOH), 1.10 (s, 3H, -CH_3) and 1.20 (s, 3H, -CH_3).

3,3-Dimethyl-2-methylidene-4-(2,2-diphenylethenyl)cyclopentanone (**90**)

A solution of **89** (3.22 g, 10 mmol) in dichloromethane (20 mL) was added dropwise to a suspension of pyridinium chlorochromate (3.23 g, 15 mmol) and sodium acetate (0.80 g, 10 mmol) in dichloromethane (20 mL). The mixture was stirred for 2 hr under an argon atmosphere at room temperature. Ether (50 mL) was added and the mixture filtered through a short pad of Florisil. The filtrate was concentrated and the residue chromatographed on silica gel. Elution with 5% ethyl acetate in hexane afforded the enone **90** (2.85 g; 90% yield): ir 1630, 1640 (olefin), 1600 (aromatic) and 1720 cm^{-1} (ketone carbonyl); nmr δ7.30 (m, 10H, aromatic, 6.00 (d, J = 10 Hz, 1H, -CH=), 5.15 (s, 1H, =C**H**H), 5.90 (s, 1H, =C**H**H), 1.10 (s, 3H, $-CH_3$) and 1.20 (s, 3H, $-CH_3$); ms M^+ 302.1672 (calcd. for $C_{22}H_{22}O$: 302.1670). Anal. Calcd. for $C_{22}H_{22}O$: C 87.37, H 7.33; Found: C 87.01, H 7.27.

Compound **90** from diol **88**

To a solution of oxalyl chloride (6.40 mL, 73 mmol) in dichloromethane (50 mL) at -78°C, was added dropwise with stirring, a solution of dimethyl sulfoxide (10.7 mL, 150 mmol) in dichloromethane (25 mL). After the addition, the mixture was stirred for an additional 30 min, under an argon atmosphere and ~~the~~ diol **88** (4.70 g, 15 mmol) in dichloromethane (20 mL) was added dropwise. After the addition the mixture was stirred for 6 hr at -78°C. Triethylamine (20 mL) in dichloromethane (20 mL) was added and the mixture was allowed to warm up gradually to room temperature overnight. It was poured into ice-cold water (200 mL) and the dichloromethane fraction separated, washed with brine and dried. Filtration and concentration gave the crude material which was chromatographed on silica gel. Elution with 5% ethyl acetate in hexane gave the enone **90** (3.63 g, 80% yield).

3,3-Dimethyl-2-(2-nitrobutyl)-4-(2,2-diphenylethenyl)-cyclopentanone (**91**)

A saturated solution of potassium carbonate in methanol (6 mL) was added to a solution of 1-nitropropane (0.57 mL, 6.45 mmol) in methanol (25 mL) with stirring. A solution of the enone **90** (1.30 g, 4.30 mmol) in methanol (15 mL) was added and stirring was continued for an additional 1 hr. Ice-cold 2N aqueous hydrochloric acid solution (100 mL) was added and the mixture extracted with chloroform (3 × 50 mL). The combined chloroform extract was dried, filtered and concentrated. The crude residue was chromatographed on a silica gel column. Elution with

10% ethyl acetate in petroleum ether afforded the minor isomer of **91** (0.40 g; 24% yield). Further elution with the same solvent system gave the major isomer of **91** (0.80 g; 47% yield). The following ir spectral data were observed for both isomers: 1735 (ketone carbonyl), 1545 (nitro), and 1600 cm^{-1} (aromatic). ms for both isomers M$^+$ 391.2141 (calcd. for $C_{25}H_{29}NO_3$: 391.2148).

The following nmr data were obtained for the minor isomer of **91**: δ7.20 (m, 10H, aromatic), 6.00 (d, J = 8 Hz, 1H, -CH=), 4.70 (m, 1H, -CHNO$_2$), 0.80 (s, 3H, -CH$_3$), 1.00 (s, 3H, -CH$_3$) and 1.00 (t, J = 8 Hz, 3H, -CH$_2$CH$_3$).

The following nmr data were obtained for the major isomer of **91**: δ7.20 (m, 10H, aromatic), 6.02 (d, J = 8 Hz, 1H, -CH=), 4.82 (m, 1H, -CHNO$_2$), 0.84 (s, 3H, -CH$_3$), 1.02 (s, 3H, -CH$_3$) and 1.04 (t, J = 8 Hz, 3H, -CH$_2$CH$_3$).

4-(1,2-Epoxy-2,2-diphenylethyl)-3,3-dimethyl-2-(2-oxobutyl)cyclopentanone (92) and 4-Formyl-3,3-dimethyl-2-(2-oxobutyl)cyclopentanone (94)

To a solution of nitroketone **91** (500 mg, 1.2 mmol) in methanol (20 mL) was added a 0.72 M solution of methanolic sodium methoxide (2 mL, 1.4 mmol). After stirring at room temperature for 30 min, the resulting solution was chilled to -78°C and a stream of ozone was bubbled through the solution. After 2 hr, the mixture was purged with argon to remove excess ozone. Methyl sulfide (2 mL) was added. The reaction mixture was allowed to warm up to room temperature and stirred overnight. It was concentrated and the residue taken up in dichloromethane, washed with brine, dried, filtered and concentrated. The crude material was chromatographed on silica gel. Elution with 10% ethyl acetate in petroleum ether afforded the diketo epoxide **92** (252 mg; 56% yield). Further elution with 15% ethyl acetate in petroleum ether gave the diketo aldehyde **94** (38 mg; 15% yield).

The following spectral data were obtained for **92**: ir 1715 (ketone carbonyl), 1740 (five-membered ketone), 1600 (aromatic) and 1250 cm^{-1} (epoxide); nmr δ7.40 (m, 10H, aromatic), 3.50, 3.60 (each d, J = 8 Hz, total 1H, -CHO-), 1.10 (t, 3H, J = 8 Hz, $-CH_2CH_3$), 0.85 and 1.20 (each s, 3/2 H each, $-CH_3$) and 0.95 and 1.00 (each s, 3/2 H each, $-CH_3$); ms M^+ 376.2039 (calcd. for $C_{25}H_{28}O_3$: 376.2039).

The following spectral data were obtained for **94**: ir 2740 (aldehyde), 1740 (five-membered ketone) and 1720 cm^{-1} (ketone and aldehyde carbonyl); nmr δ9.80 (d, J = 4 Hz, 1H, -CHO), 0.80 (s, 3H, $-CH_3$), 1.45 (s, 3H, $-CH_3$) and 1.10 (t, J = 8 Hz, 3H, $-CH_2CH_3$); ms M^+ 210.1266 (calcd. for $C_{12}H_{18}O_3$: 210.1256).

Diketo Aldehyde **94** from Diketo Epoxide **92**

A solution of **92** (310 mg, 0.83 mmol) in ether (10 mL) was added to a solution of periodic acid (1 g, 4.4 mmol) in ether (20 mL) with stirring at room temperature and under an argon atmosphere. After 3 hr, water (50 mL) was added and the ether fraction separated, dried, filtered and concentrated. The crude residue was chromatographed on silica gel. Elution with 15% ethyl acetate in petroleum ether afforded the diketo aldehyde **94** (110 mg, 63% yield).

4-(1,2-Epoxy-2,2-diphenylethyl)-3,3-dimethyl-2-(2-nitrobutyl)cyclopentanone (**95**)

A solution of m-chloroperbenzoic acid (80% purity, 1.0 g, ~5.8 mmol) in dichloromethane (20 mL) was added dropwise to a solution of nitro ketone **91** (1 g, 2.6 mmol) in dichloromethane (20 mL) at room temperature. After the addition the mixture was stirred for 3 hr at room temperature under an argon atmosphere. A 10% aqueous sodium sulfite solution (20 mL) was added and the mixture was poured into a 10% aqueous sodium bicarbonate solution (80 mL). The organic fraction was separated, washed with brine, dried and concentrated. The crude material was purified on a silica gel column, eluting with 10% ethyl acetate in hexane, to give the epoxy nitroketone 95 (0.94 g; 90% yield): ir 1740 (carbonyl), 1550 (nitro), 1600 (aromatic) and 1250 cm^{-1} (epoxide); nmr δ7.40 (m, 10H, aromatic), 4.90 (m, 1H, $-CHNO_2$), 3.50, 3.60 (each d, J = 8 Hz, total 1H, -CHO-), 0.85 and 1.40 (each s, 3/2 H each, $-CH_3$), 0.95, 1.00 (each s, 3/2 H each, $-CH_3$) and 1.10 (t, J = 8 Hz, 3H, $-CHCH_3$); ms M^+ 407.2068 (calcd. for $C_{25}H_{29}NO_4$: 407.2067).

Diketo Epoxide 92 from Nitro Keto Epoxide 95

A 1.19 M solution of sodium methoxide in methanol (1.5 mL, 1.8 mmol) was added to a solution of the nitro ketoepoxide 95 (600 mg, 1.5 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 40 min and a stream of ozone was bubbled through at -78°C for 1 hr. After purging with argon, dimethyl sulfide (2 mL) was added and the mixture allowed to warm up to room temperature and stirred overnight. It was concentrated and taken up in dichloromethane. The resulting solution was washed with brine, dried, filtered and concentrated. The crude residue was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane afforded the epoxy diketone 92 (400 mg; 71% yield). Spectral data were the same as those given for 92 on the previous page.

4-Carbomethoxy-3,3-dimethyl-2-(2-oxobutyl)cyclopentanone (93)

A solution of 0.8 M Jones reagent (9 mL) was added dropwise with stirring to a solution of the diketo aldehyde **94** (1 g, 4.8 mmol) in acetone (15 mL) at 0°C. After the addition, the reaction mixture was stirred for 45 min at room temperature. Isopropyl alcohol (5 mL) was added and the mixture filtered. The residue was washed thoroughly with acetone and the filtrate concentrated and taken up in dichloromethane (20 mL). The organic solution was extracted with 1N aqueous sodium hydroxide solution (3 × 20 mL). The combined aqueous extract was acidifed with 1N aqueous hydrochloric acid solution and extracted with dichloromethane (3 × 20 mL). The organic extracts were dried, filtered and concentrated. The crude product was dissolved in acetone (20 mL) and added to a mixture of anhydrous potassium carbonate (0.92 g) in acetone (20 mL). The mixture was stirred at room temperature under an argon atmosphere for 30 min and methyl iodide (0.8 mL) was introduced. The mixture was stirred for 24 hr and concentrated. Dichloromethane (30 mL) and water (30 mL) were added and the mixture shaken in a seperatory funnel. The organic fraction was separated, washed with water, dried, filtered and concentrated. The crude residue was purified on silica gel. Elution with 10%

ethyl acetate in petroleum ether afforded the pure diketo ester **93** (900 mg; 78% yield): ir 1745 (ester), 1730 (five-membered ketone carbonyl) and 1710 cm^{-1} (ketone carbonyl); nmr δ3.75 (s, 3H, $-CO_2CH_3$), 1.30(s, 3H, $-CH_3$), 0.70 (s, 3H, $-CH_3$) and 1.15 (t, 3H, J = 8 Hz, $-CH_2CH_3$); ms M^+ 240.3112 (calcd. for $C_{13}H_{20}O_4$: 240.3013). Anal. Calcd. for $C_{13}H_{20}O_4$: C 64.98, H 8.39; Found: C 64.95, H 8.57.

Diketo Ester 93 from Nitro Keto Olefin 91

Ruthenium dioxide (100 mg) was suspended in acetone (25 mL). A solution of sodium metaperiodate (2 g, 9.4 mmol) in water (25 mL) was added and the resulting mixture stirred at room temperature until a clear yellow solution was obtained. Sodium metaperiodate (1 g, 4.7 mmol) was added to the yellow solution and a solution of the nitro olefin **91** (1.30 g, 3.23 mmol) in acetone (15 mL) was added dropwise with stirring. The reaction mixture was stirred for 4 hr and isopropyl alcohol (15 mL) was added. After 30 min, the mixture was filtered through a sintered glass (size D) and the residue thoroughly washed with acetone. After most of the acetone had been evaporated, the aqueous solution was made basic with 1N aqueous potassium hydroxide solution and the mixture extracted with ethyl acetate (3 × 100 mL). The aqueous solution was acidified with 1N ice-cold aqueous hydrochloric acid solution and then extracted with chloroform (3 × 100 mL). The combined chloroform extract was dried, filtered and concentrated to afford the crude acid (1 g). Without purification, the acid was dissolved in acetone (20 mL) and potassium carbonate (1 g) was added. The mixture was stirred at room temperature under an argon atmosphere for 30 min followed by the addition of methyl iodide (1 mL). After stirring for an additional 24 hr, the acetone was evaporated and the residue was taken up in dichloromethane (50 mL) and washed sequentially with ice-cold dilute aqueous hydrochloric acid, water and brine. The organic fraction was dried, filtered and concentrated. The crude material was chromatographed on silica gel. Elution with 10% ethyl acetate in petroleum ether afforded the diketo ester **93** (0.45 g; 58% yield). All the spectral data were identical in all respects to those of **93** obtained previously.

7-Carbomethoxy-2,6,6-trimethylbicyclo[3.3.0]oct-1-en-3-one (**98**)

A 0.98 M solution of methanolic sodium methoxide (6.40 mL, 6.3 mmol) was added to a solution of the diketo ester **93** (1 g, 4.16 mmol) in methanol (20 mL). The mixture was refluxed under an argon atmosphere for 16 hr. After cooling to room temperature it was poured into ice-cold 1N aqueous hydrochloric acid solution (100 mL) and extracted with chloroform (3 × 40 mL). The combined chloroform extract was dried, filtered and concentrated. The crude product (1 g) was dissolved in acetone (20 mL) and added to a mixture of potassium carbonate (1.20 g) in acetone (20 mL). The mixture was stirred at room temperature for 30 min and methyl iodide (0.8 mL) was added. The reaction mixture was stirred at room temperature for 24 hr after which it was concentrated and taken up in dichloromethane (50 mL). It was washed with ice-cold 1N aqueous hydrochloric acid solution (3 × 40 mL) and then with water. The organic fraction was dried, filtered and concentrated. The crude material chromatographed on silica gel, eluting with 10% ethyl acetate in petroleum ether gave, the pure bicyclic enone 98 (0.74 g; 80% yield): ir 1700 (ketone carbonyl), 1745 (ester) and 1665 cm^{-1} (olefin); nmr δ3.75 (s, 3H, $-CO_2CH_3$), 1.75 (s, 3H, $-CH_3$), 1.10, 0.75 (both s, total 3H, $-CH_3$), 1.00 and 0.70 (both s, total 3H, $-CH_3$); ms M^+ 222.2931 (calcd. for $C_{13}H_{18}O_3$: 222.2860). <u>Anal.</u> Calcd. for $C_{13}H_{18}O_3$: C 70.24, H 8.16; Found C 70.64, H 8.40.

1-(3-Butenyl)-4-carbomethoxy-2,6,6-trimethylbicyclo[3.3.0]-octan-3-one (100).

A solution of 1.2 M 3-butenylmagnesium bromide in tetrahydrofuran (11.26 mL, 13.5 mmol) was added to a suspension of cuprous iodide (0.11 g, 0.58 mmol) in tetrahydrofuran (10 mL) at 0°C under an argon atmosphere. The mixture was stirred for 90 min and the temperature was lowered to -25°C. A solution of the bicyclic enone **98** (500 mg, 2.52 mmol) in tetrahydrofuran (10 mL) was introduced. After 10 min, the reaction was complete. The mixture was added dropwise to an ice-cold 2N aqueous hydrochloric acid solution with stirring. It was then extracted with dichloromethane (3 × 25 mL). The combined organic extract was dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 5% ethyl acetate in petroleum ether to give the 1,4-adduct **100** (440 mg; 72% yield): ir 1730 (ketone carbonyl), 1745 (ester) and 1640 cm^{-1} (olefin); nmr δ5.80 (m, 1H, -CH=), 5.00 (m, 2H, $=CH_2$), 3.70 (s, 3H, $-CO_2CH_3$), 1.05, 1.00 (both d, J = 6 Hz, total 3H, $-CHCH_3$), 1.20, 0.75 (both s, total 3H, $-CH_3$), 0.95 and 0.70 (both s, total 3H, $-CH_3$); ms M^+ 278.4011 (calcd. for $C_{17}H_{26}O_3$: 278.3941). Anal. Calcd. for $C_{17}H_{26}O_3$: C 73.35, H 9.41; Found: C 73.60, H 9.55.

7-Carbomethoxy-1-carbomethoxyethyl-2,6,6-trimethylbicyclo[3.3.0]octan-3-one (**103**)

At -78°C ozone was bubbled through a solution of the olefin **100** (590 mg, 2.1 mmol) in dichloromethane (15 mL) until a blue color was retained (50 min). A solution of triphenylphosphine (850 mg, 3.2 mmol) in dichloromethane (10 mL) was added with stirring. The mixture was allowed to warm up to room temperature and stirred overnight. It was then concentrated and the residue dissolved in acetone (25 mL). A solution of 0.8 M Jones reagent (5 mL) was added dropwise and the mixture stirred for 45 min at room temperature. Isopropyl alcohol (5 mL) was added and after 20 min, the mixture was filtered and concentrated. The crude product was dissolved in acetone (25 mL) and potassium carbonate (750 mg) was added with stirring. After 30 min, methyl iodide (0.6 mL) was introduced and the mixture was stirred under an argon atmosphere for 16 hr. Most of the solvent was evaporated and the residue taken up in dichloromethane (25 mL) and washed with ice-cold dilute aqueous hydrochloric acid solution (3 × 50 mL) and then with water. The organic fraction was dried, filtered and concentrated. Column chromatography of the crude product on silica gel, eluting with 10% acetate in petroleum ether afforded the ketodiester **103** (250 mg; 38% yield): ir 1720 (ketone carbonyl) and 1745 cm^{-1} (ester);

nmr δ3.70–3.72 (close singlets, total 6H, 2× $-CO_2CH_3$), 1.05, 1.00 (both d, J = 6 Hz, total 3H, $-CHCH_3$), 1.20, 0.75 (both s, total 3H, $-CH_3$), 0.95 and 0.70 (both s, total 3H, $-CH_3$); ms M^+ 310.3930 (calcd. for $C_{17}H_{26}O_5$: 310.3929). Anal. Calcd. for $C_{17}H_{26}O_5$: C 65.79, H 8.44; Found: C 65.82, H 8.56.

Compound 103 from Keto Olefin 100

Ruthenium dioxide (40 mg) was suspended in acetone (25 mL). A solution of sodium metaperiodate (800 mg, 3.76 mmol) in water (25 mL) was added and the mixture stirred at room temperature until a clear yellow solution was retained. Solid sodium metaperiodate (500 mg) was added to the yellow solution and a solution of the olefin **100** (500 mg, 1.80 mmol) in acetone (10 mL) was added dropwise. After the addition the mixture was stirred for an additional 4 hr followed by the addition of isopropyl alcohol (5 mL). After 30 min the mixture was filtered and the residue thoroughly washed with acetone. Most of the acetone was evaporated and the aqueous solution made basic with 1N aqueous potassium hydoxide solution. The basic solution was washed with ethyl acetate (3 × 50 mL) and the aqueous solution acidified with ice-cold dilute hydrochloric acid solution and then extracted with chloroform (3 × 80 mL). The combined organic extract was dried, filtered and concentrated. The crude acid (500 mg) was dissolved in acetone (30 mL) and potassium carbonate (500 mg) was added. After stirring at room temperature for 15 min, methyl iodide (0.6 mL) was introduced and stirring continued for 16 hr. Most of the acetone was evaporated and the crude material taken up in chloroform and washed sequentially with ice-cold dilute aqueous hydrochloric acid, [illegible]nd then brine. The chloroform fraction was dried, filtered and concentrated. The crude residue was chromatographed on silica gel, eluting with 10% ethyl acetate in petroleum ether to afford the pure keto diester **103** (360 mg; 65% yield) with the same spectral data as **103** obtained previously.

7-Carbomethoxy-1-carbomethoxyethyl-2-methoxy-2,6,6-trimethylbicyclo[3.3.0]oct-2-ene (**104**)

A solution of the keto diester **103** (106 mg, 0.34 mmol), trimethyl orthoformate (0.05 mL, 0.40 mmol) and p-toluenesulfonic acid (3 mg, 0.00015 mmol) in methanol (10 mL) was stirred at room temperature under an argon atmosphere for 24 hr. Ice-cold 10% aqueous sodium bicarbonate solution (30 mL) was added and the mixture extracted with chloroform (3 × 20 mL). The combined organic extract was dried, filtered and concentrated. The crude material was chromatographed on silica gel. Elution with 50% ethyl acetate in hexane gave the pure enol ether **104** (80 mg; 70% yield): ir 1745 cm^{-1} (ester); nmr δ3.65 (s, 6H, 2× -CO$_2$CH$_3$), 3.45 (s, 3H, -OCH$_3$), 1.50 (s, 3H, =CCH$_3$), 1.10, 0.80 (both s, total 3H, -CH$_3$), 1.00 and 0.70 (both s, total 3H, -CH$_3$); ms M$^+$ 324.1936 (calcd. for $C_{18}H_{28}O_5$: 324.1937). Anal. Calcd. for $C_{18}H_{28}O_5$: C 66.62, H 8.70; Found: C 66.81, H 8.82.

7-Carbomethoxy-1-carbomethoxyethyl-3,3-ethylenedithio-2,6,6-trimethylbicyclo[3.3.0]octane (106 and 107)

A solution of the keto diester **103** (480 mg, 1.55 mmol), 1,2-ethanedithiol (0.4 mL, 6 mmol) and boron trifluoride etherate (0.4 mL, 3 mmol) in dichloromethane (10 mL) was stirred at 0°C for 2 hr under an argon atmosphere. 2N aqueous sodium bicarbonate solution (20 mL) was added and the mixture extracted with dichloromethane (3 × 20 mL). The organic extract was dried, filtered and concentrated. The crude material was purified on a silica gel column, eluting with 2% ethyl acetate in petroleum ether, to afford the dithio ketal **107** (450 mg; 75% yield): ir 1740 cm^{-1} (ester); nmr δ3.75 (s, 6H, 2× -CO$_2$CH$_3$), 3.30 (s, 4H, -SCH$_2$CH$_2$S-), 1.20, 1.22 (both d, J = 8 Hz, total 3H, -CHCH$_3$), 0.90, 1.16 (both s, total 3H, -CH$_3$), 0.98 and 1.10 (both s, total 3H, -CH$_3$); ms M$^+$ 386.3821 (calcd. for $C_{19}H_{30}O_4S_2$: 386.5756).

Similar treatment of keto diester **86** with 1,2-ethanedithiol and boron trifluoride ethereate afforded the corresponding dithio ketal **106** in 80% yield: ir 1740 cm^{-1} (ester); nmr δ3.75 (s, 6H, 2x-CO_2CH_3), 3.30 (s, 4H, -SCH_2CH_2S-), 1.20, 1.22 (both d, J = 8 Hz, total 3H, -$CHCH_3$), 1.18 and 0.95 (both s, 3H each, -CH_3).

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